TITLE PAGE

Protocol Title:

A randomized, double-blind (sponsor unblind), placebo-controlled, multi-centred phase IIa study to evaluate the safety and efficacy of 13 weeks of once daily oral dosing of the selective androgen receptor modulator (SARM) GSK2881078 in older men and post menopausal women with COPD and muscle weakness, participating in home exercise

Protocol Number: 200182 Amendment 3

Short Title: A randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of 13 weeks of the selective androgen receptor modulator (SARM) GSK2881078 in COPD

Compound Number: GSK2881078

Sponsor Name and Legal Registered Address:

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Medical Monitor Name and Contact Information Can be found in the Study Reference Manual

Regulatory Agency Identifying Number(s):

Investigational New Drug (IND) number 125332, EudraCT 2017-001148-37

Approval Date: 11-OCT-2017

SPONSOR SIGNATORY:

11th October 2017

David Neil, MD **Date**

Clinical Development Director, FPD Therapy Area

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 3	11-OCT-2017
Amendment 2	22-AUG-2017
Amendment 1	19-MAY-2017
Original Protocol	24-MAR-2017

Amendment 3: 11-OCT-2017

Overall Rationale for the Amendment: This amendment updates the prohibited medication list, based on recent results from a study on drug interactions. It also removes inspiratory capacity as an endpoint, as well as peak oxygen uptake measurements, during the shuttle walk tests to improve participant comfort during the tests and to help standardize the tests across multiple sites. There are additional clarifications for timepoints.

Section # and Name	**Description of Change**	**Brief Rationale**
Section 1 Synopsis Section 4 Objectives and Endpoints Section 2 Schedule of Activities Section 9.2.1.3 Inspiratory Capacity Section 10.3.3	Removal of "Inspiratory capacity" as an endpoint and removal of reference to IC or Inspiratory Capacity	Equipment required to take these measurements during the shuttle walk tests is difficult to standardize across multiple sites.

Section # and Name	**Description of Change**	**Brief Rationale**
Other analyses		
Section 9.2.3.2 Shuttle Walk Tests	Removal of reference to peak VO_2	Equipment required to take these measurements is difficult to standardize across multiple sites.
Section 2 Schedule of Activities	Addition of footnotes 7 and 8 to specify timepoints for activity monitor return, as well as scheduling of optional MRI.	Clarification of timepoints for study site staff, as well as change in how exit interviews are anticipated to be conducted. Exit interviews will now be conducted by expert interviewers from a partner agency rather than trained site staff.
Section 9.1.3 Baseline (day 1) and last dose (day 90) visits	Clarification of language for scheduling of MRI scans	
Section 9.2.4 Patient Reported Outcome Assessments	Addition of language to specify timepoints when CAT, SGRQ, PGRS and PGIC will be measured. Clarification of how exit interview will be conducted (administered by experienced interviewers (by a partner agency) instead of by site staff)	
Section 2 Schedule of Activities	Removal of text: “Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, but will not constitute a protocol amendment. The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.”	This text is intended for phase I studies, therefore removed as per latest guidance, since addition of timepoints for assessments in phase II studies will constitute a protocol amendment.

Section # and Name	**Description of Change**	**Brief Rationale**
Section 5.5 Dose Justification	Adjusted drug half-life from 4-7 to 5-8 days. Revision of text so that it now reads: "Results of drug interaction study in healthy volunteers conducted with a prototype strong CYP3A4 inhibitor (itraconazole) showed that exposure to GSK2881078 was only modestly elevated when co-administered with a strong CYP3A4 inhibitor (AUC(0-∞) increased by 60% while Cmax decreased by 21%) compared to given alone. Therefore, exposure to GSK2881078 is expected to be within the safety margin at the proposed dose of 1 mg in women and 2 mg in men if a CYP3A4 inhibitor is co-administered with GSK2881078."	Information updated based on recent results from drug interaction studies that revealed much less interaction between CYP3A4 inhibitors and GSK 2881078 in healthy volunteers than previously expected from in-vitro data. Therefore, there is no reason to prohibit CYP3A4 inhibitors.
Section 6.2 Exclusion Criteria	Removal of reference to administration of strong oral or injectable cytochrome P-450 isoenzyme 3A4 (CYP3A4) inhibitors, and removal of criteria pertaining to consumption of fruit juices that are known CYP3A4 inducers (exclusion criteria 8 and previously numbered 19)	
Section 6.3.1 Meal and dietary restrictions	Removal of text that stated prohibition of "strong inhibitors" of CYP3A4, as well as removal of dietary requirements relating to these.	
Section 7.7	Removal of text referring to	

Section # and Name	**Description of Change**	**Brief Rationale**
Concomitant therapy	strong inhibitors of CYP3A4 Reiteration of prohibited medications that are listed in exclusion criterion 9 (drugs known to affect muscle mass)	
Section 6.2 Exclusion Criteria	Clarification of exclusion criteria to specify "pulmonary rehabilitation exercise program outside of inside the home"	Clarification of language to convey intent that a person participating in a formal pulmonary rehabilitation program, even if at home, would not be eligible for the study.
Section 9.2.1	Removal of reference to spirometry being measured at follow-up visit	Error in original protocol; revised wording in now consistent with the SoA.
Section 9.4 Treatment of overdose	Modification of definition of treatment overdose to any dose "above 1.0mg for females and 2.0mg for males within a 24-hour period"	Error in earlier protocol, which stated that any dose above 1.0mg would be considered an overdose.
Section 9.5.4 Clinical Laboratory Safety Assessments	Clarification that local laboratory tests conducted outside of the protocol that are clinically significant should be recorded in the "relevant section of the CRF, e.g. the SAE form."	Clarification that there is not a separate CRF page for locally recorded results, but that these should be captured within the relevant CRF form.
Section 9.5.5 MRI scans	Addition of wording: In participants who agree to the MRI scans, every effort should be made to conduct all applicable MRI scans (cardiac and liver MRI for female participants, and additionally a prostate MRI for male participants). In circumstances where it is not feasible to continue performing all the MRI scans (e.g. patient discomfort), the cardiac scan should be prioritized over the liver or prostate scans.	Clarify that cardiac MRI scans should be prioritized in case consenting study participants and/or site staff deem it unfeasible to continue to perform all relevant MRI scans in the sub-study

Amendment 2: 22-AUG-2017

Overall Rationale for the Amendment: This amendment removes the stair climb test as a secondary endpoint in the study, as this test could not be standardized across multiple sites. The requirements for vitamin D deficiency as an exclusion criteria have been removed in response to study feasibility assessments. In addition, reference to an IDMC on page 69, which was included in error.

Section # and Name	Description of Change	Brief Rationale
Section 1 Synopsis Section 4 Objectives and Endpoints	Removal of stair climb from endpoints table	Stair climb test could not be standardized for 10 steps across multiple sites
Section 2 Schedule of Activities	Stair climb test removed from table for schedule of activities	
Section 5.4 Scientific rationale for study design	Text modified to read: Incremental and endurance shuttle walk test, with reference to stair climb deleted	
Section 9.2.3.3	Stair climb section deleted	
Section 10 Section 10.1.1. Section 10.1.3 Section 10.3.3	"Stair climb power" deleted throughout main text and table column titled "Stair climb power"	
Section 1 Synopsis Section 4 Objectives and Endpoints	Removal of the "adherence to exercise program" secondary endpoint from the table in sections 1 and 4, and addition of following wording in exploratory endpoints in section 4: "Potentially explore adherence to	Whilst adherence to the home exercise program remains of interest, the home exercise program is being piloted in this study, therefore the dataset can only be explored if it is sufficiently complete.

Section # and Name	Description of Change	Brief Rationale
	exercise program (daily physical activity and thrice-weekly strengthening exercises)"	
Section 2 Schedule of Activities	Visits numbered (V1, V2, V3, V4, V5, V6, V7, V8 and V9)	Visit labels added to help ease of reference for participants and site staff
Section 2 Schedule of Activities	'x' removed from cell for Day 90 visit in the row 'Study treatment provided'	Error in original protocol; treatment is not provided at the end of treatment visit
Section 2 Schedule of Activities	Reference to whole body MRI removed and replaced with 'Cardiac and liver MRI (additionally prostate MRI in males)'	The whole body MRI is looking specifically at the heart, liver and, in males, the prostate therefore the wording was amended throughout the protocol for clarity.
Section 3.3.1	Whole body MRI replaced with cardiac MRI	
Section 4 Objectives and Endpoints	"Whole body" deleted from description of MRI	
Section 9.1.3 Baseline (day 1) and last dose (day 90) visits	Text modified to read "At some study sites, optional cardiac, liver and prostate MRI scans will be offered to eligible participants."	
Section 9.5.5 Whole Body MRI scan	"Whole body" deleted from section heading Reference to "whole body" in main text replaced with "cardiac, liver and prostate"	
Section 2 Schedule of Activities	Footnote number 2 amended: As stated in Section 8.2, if a participant decides to withdraw or is withdrawn by the responsible physician, the reasons for withdrawal and the results of any relevant tests will be recorded in	This was reworded to help clarify that only the safety assessments at the follow-up visit would be conducted in case of withdrawal from the study.

Section # and Name	Description of Change	Brief Rationale
	the CRF and the planned safety follow-up procedures will be performed, where possible. These include physical examination, 12-lead ECG, vitals, blood tests, urinalysis and concomitant medication review as listed for the follow-up visit (V9). The following text was deleted: The leg press should be prioritized over other functional assessments. Safety assessments to be collected at follow-up visits in case of study discontinuation or withdrawal of participants are as follows: physical examination, 12-lead ECG, vitals, blood tests, urinalysis and concomitant medication review as listed for the follow-up visit	
Section 5.1 Overall Design	Text modified with following additions: "Site staff will supervise performance of the initial exercises to assess which of the four exercises can be prescribed to participants, as well as setting the baseline intensity for the exercises and clarifying instructions from the home exercise Application." "Guidance for performing exercises and setting goals will be given by the home exercise Application from the baseline visit onwards, however participants will have the opportunity to raise any concerns they have with site staff."	Additional text with clarification on supervision of the home exercise program was added in response to comments from ethics committees.
Section 6.2 Exclusion	The following text was deleted: Deficient levels (<20 ng/mL) of 25-	Vitamin D deficiency is likely present in a significant portion of our target study population, and likely to pose a significant

Section # and Name	Description of Change	Brief Rationale
Criteria Page 31	OH Vitamin D Total; NOTE: Participants with insufficient (20 – 29 ng/mL) levels may be enrolled.	barrier to recruitment. Since it should not interfere with the study drug mechanism, therefore the decision was made to remove.
Section 8.2	Text added "or an exacerbation that requires treatment with oral steroids"	To clarify that any steroid use requires participants to withdraw from the study
Section 12.2 Appendix 2	"days" added after 125	Clarify duration of contraception use – error in original protocol
Section 12.3 Appendix 3	Reference to IDMC removed	Originally included in error, as there is no plan to have an IDMC for this study

Amendment 1: 19-MAY-2017

Overall Rationale for the Amendment: This amendment removes reference to measurement of lumbar bone density, as this requires an additional Dual-Energy X-ray Absorptiometry (DXA) scan to the ones for measurement of muscle mass, thus reducing radiation exposure for subjects.

Section # and Name	Description of Change	Brief Rationale
Section 3.3.1 Risk assessment	Remove reference to measurement of lumbar bone density in the risk mitigation strategy for bone effects	Not required as no longer performing DXA scans for measurement of bone density.
Section 9.2.2.1 Dual-Energy X-ray Absorptiometry (DXA)	Remove reference to measurement of lumbar bone density	• To remove additional burden on study participants in terms of time taken to perform an extra scan, as well as to reduce radiation exposure for subjects. • Error in the original protocol .

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1. SYNOPSIS

A randomized, double-blind (sponsor unblind), placebo-controlled, multi-centred phase IIa study to evaluate the safety and efficacy of 13 weeks of once daily oral dosing of the selective androgen receptor modulator (SARM) GSK2881078 in older men and post menopausal women with COPD and muscle weakness, participating in home exercise

Short Title: A randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of 13 weeks of the selective androgen receptor modulator (SARM) GSK2881078 in COPD

Rationale:

This study is the third clinical study with administration of GSK2881078 in humans, and it will be the first administration to the target population, defined as older men and post-menopausal female participants (50-75 years of age) with chronic obstructive pulmonary disease (COPD) and muscle weakness, participating in home exercise. This study will evaluate the safety and tolerability over 13 weeks of dosing in this population. This study will also evaluate the anabolic effects of GSK2881078 as measured by changes from baseline in leg strength, muscle mass, and functional measures.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• Assess the safety and tolerability of approximately 13 weeks of dosing of GSK2881078	• Safety and tolerability of GSK2881078 as assessed by clinical monitoring of blood pressure, heart rate, electrocardiogram (ECG) and laboratory safety data, as well as reporting of adverse events (AEs)
• Assess the effect of approximately 13 weeks of dosing of GSK2881078 on leg strength in older men and post-menopausal women with COPD and muscle weakness, participating in home exercise	• % change from baseline and change from baseline in maximum leg press strength following 1 repetition maximum (1- RM)
Secondary	
• Assess the effect of approximately 13 weeks of dosing of GSK2881078 on lean soft tissue mass	• Change from baseline in appendicular, and total lean mass as assessed by Dual-energy X-ray Absorptiometry (DXA)

Objectives	**Endpoints**
• Assess the effect of approximately 13 weeks of dosing of GSK2881078 on exercise capacity	• Change from baseline in total Short Physical Performance Battery (SPPB) score and times for chair rise and 4 m gait speed • Change from baseline in Constant Work Rate (CWR) duration from endurance shuttle walking test • Change from baseline in peak performance from incremental shuttle walking test
• Assess the effect of approximately 13 weeks of dosing of GSK2881078 on patient reported outcomes, levels of physical activity, activities of daily living and the patient perspective of efficacy	• Change from baseline in COPD Assessment Test (CAT) • Change in PROactive endpoints (individual components and total score) • Change in physical activity measures as assessed via an accelerometer • Patient Global Impression of Change • Patient Global Rating of Severity • Change in St George Respiratory Questionnaire-COPD (SGRQ-c) total score and domains
• Assess the effect of approximately 13 weeks of dosing of GSK2881078 on respiratory function	• Change from baseline in forced expiratory volume in 1 second (FEV1) • Change from baseline in Sniff nasal inspiratory pressure (SnIP)
• Characterise the population pharmacokinetic (PK) profile of approximately 13 weeks of dosing of GSK2881078 in older men and post-menopausal women with COPD and muscle weakness	• Model specific PK parameters of GSK2881078 (e.g., oral clearance, oral steady-state volume of distribution).

Additional exploratory analyses related to the primary and secondary endpoints will also be performed.

Overall Design:

This study is a randomized, placebo-controlled, double-blind (sponsor unblind), parallel group trial in two equal sized cohorts (male or female) of participants with COPD. Following completion of screen assessments, baseline assessments will be conducted in eligible participants and, in each cohort, the participants will be randomized 1:1 to GSK2881078 or matching placebo.

Number of Participants:

At least 100 participants with COPD and muscle weakness will be randomized (25/arm) to target approximately 80 evaluable participants (20/arm). Men and women will be recruited into separate cohorts of at least 50 participants each, with each cohort containing 1:1 allocation of placebo and GSK2881078.

Additional participants may be enrolled if the number of participants with exacerbations plus the number of participants withdrawn prematurely for other reasons is higher than anticipated (approximately 20%), based on differences in observed variability in endpoint parameters and the ability to detect a treatment effect at interim. The total sample size may be increased by up to 60 participants (approximately 15/arm). Enrolment is not expected to exceed approximately 160 total participants.

Treatment Groups and Duration:

The study will consist of a screening/baseline period of up to 30 days, a 13-week treatment period, and a 6 week (42 days) post-treatment follow-up visit. Study participation, including screening and follow-up, is not expected to exceed 6 months for participants in the study.

Study treatment will consist of two dosing cohorts (Male: placebo or 2.0 mg once daily of GSK2881078; Postmenopausal female: placebo or 1.0 mg once daily of GSK2881078). All participants will take their first dose of study treatment in the clinic following randomization. Participants will be dosed without regards to food intake.

2. SCHEDULE OF ACTIVITIES (SOA)

Procedure	**Screening** V1 (up to 30 days before Day 1)	**V2** Day -9	**Treatment Period (13 weeks)**							**Follow-up**[2] V9 (42 days post last dose)	**Notes**
			V3 Baseline Day 1	V4 Day 14	V5 Day 28	V6 Day 56	V7 Day 80	V8 Last dose 90	Unscheduled visit [1]		
Visit window (days)	- 30 to -11	-11 to -7	-2 to day 1	12 - 16	24 – 32	52-60	76 - 84	85 – 91		126- 140	There should be an attempt to conduct all assessments for a visit within a single day[3].
Informed consent	X										Obtained prior to performing any study-related procedures.
Inclusion and exclusion criteria	X										
Demography/ medical/medication/ drug/ alcohol history/ PD disease staging	X										
Full physical examination	X								X	X	
Brief physical exam			X	X	X	X		X			
12-lead ECG	X		X	X	X	X		X	X	X	
Vital signs	X		X	X	X	X		X	X	X	
HIV, Hepatitis B and C screening	X										If test otherwise performed within 3 months prior to first dose of study treatment, testing at screening is not required
Hepatitis C viral RNA PCR									X		If evidence of Hepatitis C antibodies at screening visit, then Hepatitis C viral RNA PCR required to exclude active infection. This sample is not needed if Hepatitis C screening is negative.

Procedure	**Screening** V1 (up to 30 days before Day 1)	**V2** Day -9	**Treatment Period (13 weeks)**							**Follow-up**[2] V9 (42 days post last dose)	**Notes**
			V3 Baseline Day 1	V4 Day 14	V5 Day 28	V6 Day 56	V7 Day 80	V8 Last dose 90	Unscheduled visit [1]		
Haematology (Full blood count)/ Clinical Chemistry (Creatinine, urea and electrolytes, liver function tests, glucose)	X		X	X	X	X		X	X	X	Participants should fast overnight for at least 8 hours prior to collection of these samples.
HbA1c	X							X			
hsCRP, Fibrinogen			X					X		X	
25-OH Vitamin D Total, 25-OH Vitamin D2, 25-OH Vitamin D3	X							X		X	
Lipid panel	X		X	X	X	X		X		X	
Genetic sample			X								Obtain after participant is randomized. **Informed consent to obtain the genetics sample** must be obtained before collecting a sample.
Pharmacokinetic sampling				X[4]	X[4,5]	X[6]		X[4]	X		Times of dose administration for the two doses immediately preceding a PK sample should be accurately recorded.
Reproductive Tissue Biomarkers			X		X	X		X		X	
PSA	X		X		X	X		X		X	For male participants only
Bone Biomarkers			X			X		X		X	
Exploratory Biomarkers			X	X	X	X		X		X	
Urinalysis	X		X					X	X	X	
DXA			X		X	X		X	X	X	
Spirometry	X		X			X		X			Follow ATS/ ERS guidelines [Celli, 2004] and Quanjer reference equation [Quanjer, 2012].

Procedure	**Screening** V1 (up to 30 days before Day 1)	**V2** Day -9	**Treatment Period (13 weeks)**							**Follow-up**[2] V9 (42 days post last dose)	**Notes**
			V3 Baseline Day 1	V4 Day 14	V5 Day 28	V6 Day 56	V7 Day 80	V8 Last dose 90	Unscheduled visit [1]		
Sniff Nasal Inspiratory Pressure	X		X			X		X			
Leg strength	X		X		X	X		X		X	
Handgrip strength	X		X					X			
Short Physical Performance Battery	X		X		X	X		X		X	
Incremental Shuttle Walk Test		X	X					X			Practice incremental shuttle walk test conducted at day -9
Endurance Shuttle Walk Test			X					X			
COPD Assessment Test			X			X		X			
St George Respiratory Questionnaire COPD (SGRQ-c)			X					X			
Patient Global Rating of Severity			X					X			
Patient Global Impression of Change				X	X	X		X		X	
Daily PROactive Physical Activity in COPD instrument and Physical Activity Monitor	X	X[7]				X	X[7]				Physical activity monitor dispensed at screening, day -9, day 56 and day 80 visits. Activity monitor should be worn for 7 days at each timepoint and returned at the next visit.
Monitored home exercise program		X	X	←==========				X			Participants will receive training for the exercise program at Day -9, and will formally begin exercises on day 1
Patient exit interview										X	
Randomization			X								All Baseline assessments must be obtained prior to randomization.
Study treatment provided to participant			X		X	X					The subject should take their first dose of study treatment in the clinic after randomization.

Procedure	**Screening** V1 (up to 30 days before Day 1)	**V2** Day -9	**Treatment Period (13 weeks)**							**Follow-up**[2] V9 (42 days post last dose)	**Notes**
			V3 Baseline Day 1	V4 Day 14	V5 Day 28	V6 Day 56	V7 Day 80	V8 Last dose 90	Unscheduled visit [1]		
Study treatment			X	←==========→				X			Participants should dose study treatment in the clinic at each clinic visit during the treatment period.
Study treatment accountability by study site			X	X	X	X		X			The required counting of pills by site staff to check compliance is not considered redispensing the study medication.
AE review			X	←==========→						X	
SAE review			X	←==========→						X	
Concomitant medication review			X	←==========→						X	
Optional sub-study measures											
Cardiac and liver MRI (additionally prostate MRI in males)			X[8]					X[8]			MRI is an optional assessment undertaken at participating centres only.

ECG= Electrocardiogram; HIV= Human Immunodeficiency Virus; PK= Pharmacokinetic; PSA= Prostate Specific Antigen; DXA= Dual-energy X-ray Absorptiometry; AE= Adverse Event; SAE= Serious Adverse Event.

1. An unscheduled clinic visit may occur at any time if the investigator believes an unscheduled visit is clinically warranted. Individual listed assessments are optional and are performed as needed to follow unresolved findings of clinical concern. Note: The "Unscheduled visit" case report form (CRF) form should be completed as soon as possible following the Unscheduled visit.
2. As stated in Section 8.2, if a participant decides to withdraw or is withdrawn by the responsible physician, the reasons for withdrawal and the results of any relevant tests will be recorded in the CRF and the planned safety follow-up procedures will be performed, where possible. These include physical examination, 12-lead ECG, vitals, blood tests, urinalysis and concomitant medication review as listed for the follow-up visit (V9).
3. Attempt to conduct all visits within a single day however the baseline (day 1) and last dose (day 90) visits may require subjects to visit the study centre on more than one day in order to complete MRI and DXA scans, and possibly other assessments. These

scans, and any other assessments, should be conducted within the specified visit window, and prior to randomization at the baseline visit. Further details on the suggested order of assessments will be given in the SRM.

4. Take PK sample prior to dosing in the clinic
5. Take PK sample 1-4 hours post-dose (sites should try and ensure that a range of times are sampled within this time window for different participants, i.e. all PK samples should not be taken at 1 hour post dose or 2 hours post dose).
6. Take PK sample 5-8 hours post-dose (as above, sites should try and ensure that a range of times are sampled within this time window for different participants).
7. At V3 Baseline Day 1 and V8 Last dose 90, the patients will return the Daily PROactive Physical Activity in COPD Instrument and the Physical Activity Monitor to the site. Patients will not be dispensed the Daily PROactive Physical Activity in COPD Instrument and the Physical Activity Monitor at the end of these visits.
8. All MRI Scans (Cardiac MRI, Liver MRI and, if applicable, Prostate MRI) should preferably be scheduled on the same day. Acquisition of the Cardiac MRI should be prioritized above the other two scans if it becomes unfeasible to perform all the MRI scans.

The following points must be noted:

- If assessments are scheduled for the same nominal time, THEN the assessments should occur in the following order:
    i. vital signs
    ii. 12-lead ECG
    iii. blood draws.

Note: The timing of the assessments should allow the blood draw to occur at the time specified in the SoA

3. INTRODUCTION

GSK2881078 belongs to a novel class of non-steroidal, Selective Androgen Receptor Modulators (SARMs) and is under investigation by GlaxoSmithKline (GSK) for treatment of impaired mobility, disability and functional limitation in older men and post-menopausal women with muscle weakness associated with Chronic Obstructive Pulmonary Disease (COPD). Conditions such as COPD, congestive heart failure, and chronic kidney disease can demonstrate significant muscle wasting and associated functional impairment, especially in advanced states. Physical therapy and exercise have been shown in these conditions to increase muscle mass and improve physical function. The use of the natural steroidal androgen receptor agonist, testosterone, has also been shown in these conditions to induce similar benefits, but such use is limited by prostate effects and androgenic effects. A non-steroidal, selective androgen receptor agonist can potentially act positively on muscle and bone while not adversely affecting the prostate gland in men, or inducing hirsutism or virilization in women.

3.1. Study Rationale

This study is the third clinical study with administration of GSK2881078 in humans, and it will be the first administration to the target population, defined as older men and post-menopausal female participants (50-75 years of age) with COPD and muscle weakness, participating in home exercise. This study will evaluate the safety and tolerability over 13 weeks of dosing in this population. This study will also evaluate the anabolic effects of GSK2881078 as measured by changes from baseline in leg strength, muscle mass, and functional measures.

3.2. Background

Impaired physical function and muscle dysfunction are a major consequence of COPD and may be associated with increased mortality, poor quality of life, and increased health care use. Physical therapy and exercise have been shown to increase muscle mass and improve physical function in participants with COPD [Maltais, 2014]. Increased muscle mass and improved physical function have also been shown with the natural steroidal androgen receptor agonist testosterone in participants with COPD [Atlantis, 2013]. However, use of testosterone to treat muscle dysfunction in participants with COPD may be limited due to adverse effects in both men and women. A non-steroidal, selective androgen receptor agonist can potentially act positively on muscle while avoiding unwanted effects seen with testosterone (e.g., prostate hypertrophy in men or hirsutism or virilization in women). Currently, there are no medications approved by the United States Food and Drug Administration (FDA) for the treatment of muscle wasting disorders of any aetiology.

The scientific opportunity for the treatment of muscle-wasting and associated disorders is presented through the development of non-steroidal molecules that act via the androgen receptor in a cofactor/cellular/tissue-selective manner. SARMs bind to the androgen receptor inducing a unique receptor conformation which allows only certain co-activator and co-repressor proteins to interact. These unique receptor-cofactor ensembles confer differential regulation of target genes and other receptor-mediated pathways. The

differential activity allows SARMs to function as potent androgens in target tissues such as muscle and bone, but function as antagonists, or partial agonists, in other tissues or organs such as the prostate or skin. Further, an appropriately selective SARM could be given to post-menopausal women without inducing hirsutism or virilization, which occurs with steroidal androgen receptor modulators.

While no SARM has been approved for clinical use, there is growing clinical experience with this class of compounds. Enobosarm has been through a series of clinical studies and recently finished a Phase 3 program evaluating the efficacy for treatment of muscle loss and functional impairment in cancer cachexia [Dalton, 2011; Dobs, 2013]. Although the phase 3 study for Enobosarm did not show an improvement in stair climb power (co-primary endpoint), there appeared to be a consistent effect of enobosarm on muscle mass and strength in study participants in phase 2 trials. An additional SARM, LGD-4033, has shown no apparent safety signals and has demonstrated an increase in lean body mass (LBM) in repeat dosing in healthy male volunteers [Basaria, 2012]. GSK also has clinical experience with SARM compounds, GSK971086 and GSK2849466. These compounds were evaluated in first-time-in-human studies in healthy male volunteers, both showing expected effects on biomarkers and no safety signals in studies less than 3 weeks. However, both of these compounds were discontinued because of unexpected toxicity observed in longer preclinical safety studies.

A detailed description of the chemistry, pharmacology, efficacy, and safety of GSK2881078 is provided in the Investigator's Brochure (IB).

3.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of GSK2881078 may be found in the IB.

3.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) GSK2881078		
Elevation of Alanine Aminotransferase (ALT) and other liver function tests (AST, bilirubin, total and direct).	This has been observed in a variety of SARMs and was observed (minimal) in the 14-day and 13-week rat toxicity studies with administered GSK2881078. One subject had elevations of Liver Function Tests (LFTs) in Phase 1a, but it was unclear if this was related to drug. Transient elevations in ALT without concomitant changes in bilirubin were observed in Phase 1b.	Monitoring of liver function tests will be in place at all clinic visits. This study will use follow up procedure that were used in Phase I of development of GSK2881078 for participants who have met liver stopping criteria, as detailed in Section 8.1.1 of this protocol.
Effects on reproductive organs/tissues: Men – testes, epididymis, and prostate gland Women – ovaries and uterus	These are recognized effects of SARM pharmacology and show recovery on discontinuation of dosing. Test article-related organ weight and/or microscopic changes were observed in the gonads and other associated reproductive tissues in rat 14-day and 13-week toxicity studies administered GSK2881078. All test article-related microscopic findings were reversible after a 4- or 8- week off dose period. Test article-related effects were observed in male mating, fertility, gonadal function, and male-mediated development in a male rat fertility study. In phase I studies, all male subjects dosed with	Males with PSA levels >4.0 ng/mL will be excluded. Females will be post-menopausal. Participants will be monitored at baseline, Day 28, Day 56, Day 89 and follow-up for changes in the following levels: • luteinizing hormone • follicle stimulating hormone • testosterone • free testosterone (calculated) • estradiol

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	GSK2881078 displayed reversible reductions in testosterone. No changes in PSA were recorded. Reversible reductions in sex hormone binding globulin were observed in both men and women. There were no clinically significant changes in FSH, LH, estradiol or progesterone.	• dihydrotestosterone • sex hormone binding globulin
Lowering of High-Density Lipoprotein (HDL) levels - A class effect of SARMs	All subjects dosed with GSK2881078 exhibited a reduction in HDL Cholesterol in Phase I studies. This reduction exhibited a dose response, with evidence of maximal pharmacology at a reduction of approximately 30-40% from baseline. This reduction was accompanied by a similar reduction proportionally in ApoA1. In all cases HDL Cholesterol returned to baseline on discontinuation of dosing.	Monitoring lipid profiles to confirm decreases seen on treatment, and whether lipid parameters return to baseline following discontinuation of study treatment. Lipid panels will be monitored at baseline, Day 56, Day 89 and at follow-up.
Bone effects	Minimal trabecular atrophy was observed in female rats at all doses in a 13- week toxicity study. This finding was not observed in male rats or dogs of either sex after 13 weeks of GSK2881078 administration.	Bone turnover markers will be measured at baseline, Day 56, Day 89 and at follow-up. Bone biomarkers will include: • procollagen type I N propeptide (s-PINP) for formation • C-terminal telopeptide of type I collagen (s-CTX)
Anabolic abuse	Since this compound builds lean body mass, there is potential risk for anabolic abuse through illicit use of the drug by body builders.	Use of compound will be restricted to participants enrolled in study. Sites will have in place secure storage for compound supply. Sites to confirm restricted use of compound by enrolled participants at each study visit. Sites will be inspected for secure storage.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Risks to women and foetal risk	Risks to women of possible androgenic effects from exposure to study compound by handling or by seminal exposure. In pregnant women, risk of exposure to compound during period of fetal reproductive differentiation.	Women who are not post-menopausal should avoid handling or ingestion of the study medication (capsules). Male participants should always use condom with female partners of childbearing potential. Sites to confirm compliance with guidelines by participants at each study visit.
Increase in absolute (not relative) heart weight	There is a theoretical risk that the anabolic effects of GSK2881078 are not only selective for striated skeletal muscle, and that there is an increase in cardiac muscle size. There are no pre-clinical or clinical data to support this risk.	Cardiac MRI will be carried out on a small subset of patients; the scan will be used to evaluate changes from baseline in cardiac size, structure and function in the treatment arm.
Study Procedures		
Risk of cardiac angina from incremental or endurance shuttle walk exercise tests	There is high incidence of cardiovascular comorbidity in COPD; undiagnosed disease may manifest during exercise tests	Physical exam, medical history and baseline ECGs will assess cardiovascular risk. Participants with a history of unstable angina will be excluded. Exercise tests will only be carried out under the supervision of suitably trained study personnel as detailed in the SRM.
Other		
None		

3.3.2. Benefit Assessment

Potential benefits of receiving GSK2881078 include gaining muscle mass, which may increase muscle strength and physical function, and may improve glycaemic control.

Participation in this study will contribute to the process of developing a new therapy in an area of unmet need, namely in people with COPD who suffer from muscle weakness.

Study participants will undergo medical evaluations and assessments associated with study procedures, which may be of benefit in identifying or monitoring COPD related features, e.g. physical examination, ECGs and laboratory tests can identify individuals at risk of cardiac comorbidity.

3.3.3. Overall Benefit: Risk Conclusion

Based upon review of available data from the FTIH study and the known and possible risks of therapy with GSK2881078, the potential therapeutic benefits of the SARM GSK2881078 for participants diagnosed with COPD and who suffer from muscle weakness warrant further study of the compound. Therefore, it is appropriate to proceed with this Phase II trial with medical supervision as outlined within this protocol.

4. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• Assess the safety and tolerability of approximately 13 weeks of dosing of GSK2881078	• Safety and tolerability of GSK2881078 as assessed by clinical monitoring of blood pressure (BP), heart rate, electrocardiogram (ECG) and laboratory safety data, as well as reporting of adverse events (AEs)
• Assess the effect of approximately 13 weeks of dosing of GSK2881078 on leg strength in older men and post-menopausal women with COPD and muscle weakness, participating in home exercise	• % change from baseline and change from baseline in maximum leg press strength following 1 repetition maximum (1- RM)
Secondary	
• Assess the effect of approximately 13 weeks of dosing of GSK2881078 on lean soft tissue mass	• Change from baseline in appendicular, and total lean mass as assessed by Dual-energy X-ray Absorptiometry (DXA)

Objectives	**Endpoints**
• Assess the effect of approximately 13 weeks of dosing of GSK2881078 on exercise capacity	• Change from baseline in total Short Physical Performance Battery (SPPB) score and times for chair rise and 4 m gait speed • Change from baseline in Constant Work Rate (CWR) duration from endurance shuttle walking test • Change from baseline in peak performance from incremental shuttle walking test
• Assess the effect of approximately 13 weeks of dosing of GSK2881078 on patient reported outcomes, levels of physical activity, activities of daily living and the patient perspective of efficacy	• Change from baseline in COPD Assessment Test (CAT) • Change in PROactive endpoints (individual components and total score) • Change in physical activity measures as assessed via an accelerometer • Patient Global Impression of Change • Patient Global Rating of Severity • Change in St George Respiratory Questionnaire-COPD (SGRQ-c) total score and domains
• Assess the effect of approximately 13 weeks of dosing of GSK2881078 on respiratory function	• Change from baseline in forced expiratory volume in 1 second (FEV1) • Change from baseline in Sniff nasal inspiratory pressure (SnIP)
• Characterise the population pharmacokinetic (PK) profile of approximately 13 weeks of dosing of GSK2881078 in older men and post-menopausal women with COPD and muscle weakness	• Model specific PK parameters of GSK2881078 (e.g., oral clearance, oral steady-state volume of distribution).

Objectives	Endpoints
• **Exploratory**	
• Assess the safety of 13 weeks of dosing of GSK2881078 in older men and postmenopausal women in a subset of up to 15 male and 15 female participants with COPD via magnetic resonance imaging (MRI)	• Changes from baseline in hepatic, prostate (males) and cardiac structure and function as assessed via MRI. Further exploratory analyses may include changes from baseline in size of inspiratory muscles and/ or other organs.
• Conduct semi-structured exit interviews	• Gain further insights into the participants' experience with study treatment and their participation in the trial.
• Assess the effect of 13 weeks of dosing of GSK2881078 in older men and postmenopausal women on peripheral strength	• Changes from baseline in handgrip strength • Potentially explore adherence to exercise program (daily physical activity and thrice-weekly strengthening exercises)

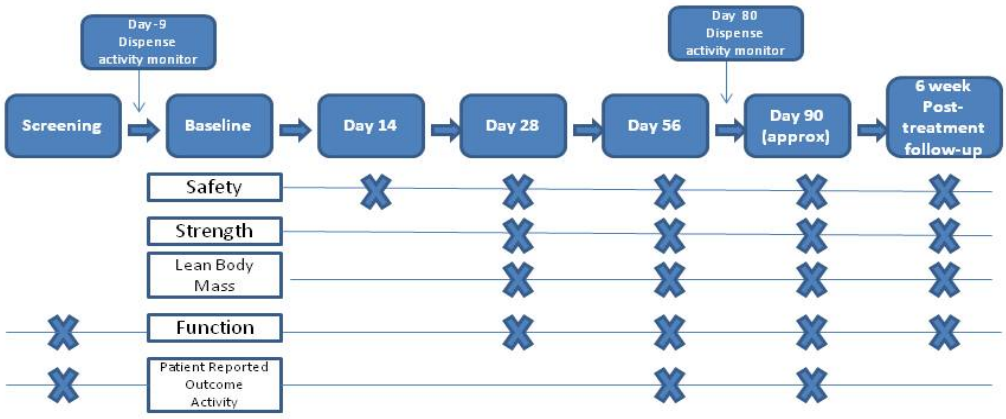
Additional exploratory analyses related to the primary and secondary endpoints will also be performed.

5. STUDY DESIGN

5.1. Overall Design

This study is a randomized, placebo-controlled, double-blind (sponsor unblind), parallel group, multi-center phase IIa trial in two equal sized cohorts (male or female). Following completion of screen assessments, baseline assessments will be conducted in eligible participants and, in each cohort, the participants will be randomized 1:1 to GSK2881078 or matching placebo.

Figure 1 Study Schematic



This study will assess the effect of GSK2881078 on physical strength and function after 13 weeks of treatment. The placebo group will serve as an appropriate control group in order to limit evaluation bias in the study endpoints. No suitable active comparator is currently available. Both treatment and control groups will be asked to participate in a standardized home exercise program. Study treatment will consist of two dosing cohorts (Male: placebo or 2.0 mg of GSK2881078; Postmenopausal female: placebo or 1.0 mg of GSK2881078). All participants will take their first dose of study treatment in the clinic following randomization, and will continue on a once daily dose for the duration of the treatment period. Participants will be dosed without regards to food intake. All doses should be administered in the clinic on study visit days during the treatment period. Time of dosing for the 2 doses prior to sample collection should be recorded and PK samples should be collected as specified in the SoA (Section 2).

The study will consist of a screening/baseline period of up to 30 days, a 13-week treatment period, and a 6-weeks post-treatment follow-up visit as described in the Time and Events table (Section 2). Unscheduled visits may be performed as needed to conduct optional assessments required to follow unresolved findings of clinical concern.

Participants will participate in a screening visit within 30 days prior to randomization and baseline assessments. Prior to randomization, eligible participants will need to have a functional muscle deficit as defined by the Short Physical Performance Battery (SPPB) inclusion criterion (Section 6.1). Eligible participants will also have physical activity and patient reported outcomes (PROs) recorded prior to baseline, and will need to

demonstrate compliance with completion of the electronic diaries and wearing the activity monitor prior to randomization.

The selection of individual medications and dosages for the treatment of COPD is left to the discretion of the investigator, although it is recommended that treatment regimens conform to current, local, national standard of care, and that treatment is optimized prior to screening with no further changes to treatment anticipated between the randomization visit and the end of the study.

Eligible participants will be randomized as described above following completion of the Baseline assessments. Participants will be sent home with a 42-day supply of study medication. Participants will be asked to return to the clinical unit on approximately days 14, 28, 56, 80 and 90 as specified in the SoA (Section 2) Participants will be resupplied with study treatment at the Day 28 and 56 visits.

All visits should be conducted in a single day within the study visit window (Section 2). Participants will be provided a meal between completion of fasting labs and start of other study assessments.

All participants will be asked to participate in a home exercise program reflecting usual care (e.g. a pulmonary rehabilitation program). The home exercise program will consist of daily walking, along with several resistance or weight-bearing exercises, such as bicep curls, upright rows, step ups, and a sit-to-stand manoeuvre, as allowed by site staff at screening. Site staff will supervise performance of the initial exercises to assess which of the four exercises can be prescribed to participants, as well as setting the baseline intensity for the exercises and clarifying instructions from the home exercise Application. Home exercises will be monitored with the use of a consumer-based activity monitor during the activities outside the clinic [Mitchell, 2014]. Guidance for performing exercises and setting goals will be given by the home exercise Application from the baseline visit onwards, however participants will have the opportunity to raise any concerns they have with site staff. See Study Reference Manual (SRM) for additional detail.

A physical activity monitor will be worn for 7 days at screening for eligible participants,7 days after the Day -9 visit, for 7 days after the Day 56 visit, and for 7 days following the day 80 visit. During those periods, participants will rate their physical activity on a daily basis by completing the PROactive eDiary. In addition, participants will be asked to complete additional questionnaires CAT which assesses the impact of COPD on a patient's life, Patient Global Rating of Severity (PGRS), Patient Global Impression of Change (PGIC) during scheduled clinic visits as specified in the SoA Time and Events table (Section 2).

Participants will return to the clinic for a follow-up visit 42 days (±7 days) after the final dose of study treatment to undergo safety evaluations and final functional assessments. In addition, all remaining study medication that was not returned at the last treatment visit (i.e., Day 90) will be returned to the clinical unit for final drug accountability.

The study duration, including screening and follow-up, is not expected to exceed 6 months for participants in the study.

Unblinded data will be reviewed in-stream by the GSK clinical study team and the safety review team (SRT). If, at any time, the 2.0 mg dose in men or the 1.0 mg dose in women, has a safety signal of clinical concern, treatment will be stopped.

An interim analysis for the assessment of futility is planned. It is anticipated that a formal declaration of futility would not be made before at least 10 participants per group have completed dosing and all key study assessments. However, if at any time it is determined that the probability of a successful outcome is sufficiently low, recruitment could be stopped. The primary endpoint for assessment of futility is strength. However, the decision to continue or stop recruitment will be made by the unblinded GSK clinical study team and Safety Review Team (SRT) based on the evaluation of all available safety, efficacy, and tolerability data. Such decisions will be based on the totality of the data (including strength, lean mass, function, safety, and tolerability). See Section 10 for more detail. The feasibility of making a decision to stop recruitment based on a futility analysis will be dependent on the recruitment rate. Futility will be evaluated separately for female and male participants.

Based on the observed variability and treatment effects at an interim analysis, the sample size may be increased to improve the precision of the estimates of treatment effects. This will be evaluated separately for males and females. The sample size may be increased by up to 15 subjects/arm.

5.2. Number of Participants

At least 100 participants with COPD and muscle weakness will be randomized (25/arm) to target approximately 80 evaluable participants (20/arm). Men and women will be recruited into separate cohorts of at least 50 participants each, with each cohort containing a placebo and GSK2881078 arm. Sample size consideration and assumptions are discussed in more detail in Section 10.1.1 .

Within each cohort, equal numbers of male and female participants will be randomized in a 1:1 allocation using a central randomization system to receive one of the planned treatment regimens listed below:

Male participants: Placebo or 2.0 mg GSK2881078
Female participants: Placebo or 1.0 mg GSK2881078

Additional participants may be enrolled if the number of participants with exacerbations plus the number of participants withdrawn prematurely for other reasons is higher than anticipated (approximately 20%), or the precision of the estimates of the treatment effects based on the observed variability and treatment effect at an interim analysis. The total sample size may be increased by up to 60 participants (approximately 15/arm). Enrolment is not expected to exceed approximately 160 total participants.

5.3. Participant and Study Completion

A participant is considered to have completed the study if they have completed all phases of the study including the follow-up visit.

The end of the study is defined as the last participant's last visit.

5.4. Scientific Rationale for Study Design

This study is designed as a proof of concept study to evaluate the anabolic potency of GSK2881078 using leg strength as the primary endpoint. This endpoint has been used in several studies with testosterone, including dose response studies in men, with a good correlation between anabolic potency and change from baseline in leg strength [Bhasin, 2005]. In addition, functional endpoints, defined as short physical performance battery, incremental and endurance shuttle walk, and PRO, are included. The duration of the study, 13 weeks, is adequate to reach a near plateau effect in leg strength [Sheffield-Moore, 2011].

Based on studies with testosterone [Casaburi, 2004 ; Sheffield-Moore, 2011] it is estimated that a minimum of 2kg increase in total LBM would be needed to achieve a meaningful improvement in leg strength. The amount of muscle mass change required to elicit meaningful functional change in humans is unknown.

5.5. Dose Justification

GSK2881078 has been administered to 154 subjects across two clinical pharmacology studies in healthy human volunteers (study 200181 in healthy young men and post-menopausal women and study 204699 in healthy elderly men and post-menopausal women). PK and pharmacodynamic (PD) of GSK2881078 have been evaluated over the range of 0.05 mg to 4.0 mg in men and 0.24 mg to 1.5 mg in women for up to 56 days duration. PK data suggests that GSK2881078 has a long half-life in the range of 5-8 days.

From an efficacy and safety standpoint, significant gains in lean mass from baseline have been observed across the dose levels evaluated to date with women showing greater sensitivity to the anabolic stimulus than men. Total mean body lean mass accrual in phase I studies ranged between 0.43kg and 3.39kg for women and 0.87kg and 1.72kg for men across different doses. PD analysis from phase I suggests that a 1.0mg dose in women would achieve a total lean mass accrual of approximately 2kg. In males, a plateau appeared to have been reached between the 1.5mg and 4mg doses, therefore a dose of 2.0mg was chosen.

From a safety coverage standpoint, the exposures as measured by area under the concentration-time curve over the dosing interval (AUC[0-τ]) at the 2.0 mg dose in men and 1.0 mg dose in postmenopausal women represent <50% of NOAEL established in the 13-week dog study in both genders, respectively. The dose limiting toxicity observed in the 13-week dog study was at 2 mg/kg/day, the highest dose given. At 2 mg/kg/day on Day 91, mean systemic exposure values were area under the concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration within a participant across all treatments ($AUC_{0-t)}$ 10.8 µg.h/mL for male dogs and 6.46 µg.h/mL for female dogs, and maximum observed concentration ($C_{max)}$ 0.778 µg/mL for male dogs and 0.536 µg/mL for female dogs).

GSK2881078 has been generally well tolerated with no SAEs noted. Adverse events of potential clinical significance primarily related to clinical chemistry including elevations of liver function tests, HDL cholesterol lowering, and suppression of testosterone and sex hormone binding globulin (SHBG). Elevations of liver function tests appeared transient, and changes in HDL, testosterone and SHBG were reversible on treatment discontinuation. Results of drug interaction study in healthy volunteers conducted with a prototype strong CYP3A4 inhibitor (itraconazole) showed that exposure to GSK2881078 was only modestly elevated when co-administered with a strong CYP3A4 inhibitor (AUC(0-∞) increased by 60% while Cmax decreased by 21%) compared to given alone. Therefore, exposure to GSK2881078 is expected to be within the safety margin at the proposed dose of 1 mg in women and 2 mg in men if a CYP3A4 inhibitor is co-administered with GSK2881078.

6. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, or participant safety. Therefore, adherence to the criteria as specified in the protocol is essential. Specific information regarding warnings, precautions, contraindications, AEs, and other pertinent information on the GSK investigational product or other study treatment that may impact participant eligibility is provided in the IB/IB supplement(s).

6.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Participant must be 50 to 75 years of age inclusive, at the time of signing the informed consent.
2. Male and/or female:

   a. Male participants:

   A male participant with a partner who is a woman of child bearing potential (WOCPB) must agree to use contraception as detailed in Appendix 2 of this protocol during the treatment period and for at least 5 half-lives of study medication have passed after the last ingested dose [125 days, corresponding to time needed to eliminate study treatment for both genotoxic and teratogenic study treatments ***plus*** an additional 90 days (a spermatogenesis cycle) for study treatments with genotoxic potential] after the last dose of study treatment and refrain from donating sperm during this period.

   b. Female participants:

   A female participant is eligible to participate if she is post-menopausal and not a woman of childbearing potential (WOCBP) as defined in Appendix 2. Note: Postmenopausal is defined as 12 months of spontaneous amenorrhea [in questionable

cases a blood sample with simultaneous follicle stimulating hormone (FSH) levels consistent with menopause (refer to laboratory reference ranges for confirmatory levels), or be >60 years of age].

3. Confirmed diagnosis of COPD in accordance with the ATS/ERS criteria [Celli, 2004] with a post-bronchodilator FEV_1/ forced vital capacity (FVC) < 0.70 AND 30% ≤ FEV_1%predicted ≤65% of predicted normal value calculated at Screen using the Quanjer reference equation [Quanjer, 2012].
4. Short Physical Performance Battery (SPPB) with ALL of the following:
   - Timed chair stand score ≥1 AND ≤3
   - No score of "0" on any component of the SPPB (i.e., gait speed, balance, or timed chair stand)
5. Body Mass Index (BMI) within the range 18 - 32kg/ m^2 (inclusive), where BMI = (weight in kg) / $(\text{height in meters})^2$
6. Current smokers OR former smokers with a cigarette smoking history of ≥10 pack years (1 pack year =20 cigarettes smoked per day for 1 year or equivalent). Former smokers are defined as those who have stopped smoking for at least 6 months prior to Baseline.
7. Participants must be able to read and write in the language used for the provided electronic diary and be able to operate an electronic device to a level that allows them to complete an electronic diary on a daily basis.
8. Participants participating in a structured exercise program must be willing to convert their current exercise program to the home exercise program used in this study.
9. Capable of giving signed informed consent as described in Appendix 3 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

6.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Participants with a history of myocardial infarction, angina, congestive heart failure exacerbation, hospitalization for cardiac aetiology, stroke or transient ischemic attack in the past 12 months.
2. Neurologic, musculoskeletal, osteoarthritis, or any other condition that in the opinion of the investigator limits participant's ability to complete study physical assessments.
3. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).
4. Participants with a history of cholecystectomy.
5. Participants with a history of malignancy that is not in complete remission for at least 2 years or 1 year for non-melanoma skin carcinoma.
6. Participants with a family history of early onset prostate cancer or familial prostate cancer (multiple family members).

7. Diseases known to cause malabsorption of protein or energy, such as inflammatory bowel disease, celiac disease, pancreatic insufficiency, etc.

Prior/Concomitant Therapy

8. Current or planned administration of cholestyramine or strong oral or injectable cytochrome P-450 isoenzyme 3A4 (CYP3A4) inducers (refer to Section 7.7 for a list of prohibited medications).
9. Current or planned use of any prescription drugs known to affect muscle mass, including androgen supplements, anti-androgens (such as LHRH agonists), anti-estrogens (tamoxifen, etc.), recombinant growth hormone, megesterol, etc.
10. Use of oral steroids concurrently or within 4 weeks preceding the screening visit.

Prior/Concurrent Clinical Study Experience

11. The participant has participated in a clinical trial and has received an investigational product within the following time period prior to randomization in the current study: 30 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer).

Diagnostic assessments

12. Participants with values outside the specified ranges for the following Key Clinical Laboratory Tests must be excluded from the study:
    - Renal function: Glomerular Filtration Rate (GFR) <30 (mL/min/1.73 m^2) using formulae provided in the Study Reference Manual (SRM). Note: Participants receiving dialysis are excluded from this study.
    - Metabolic – HbA1c >7.5%.
    - ALT >2xULN and bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
    - Haematology – Haemoglobin <10.0 g/dL at screening
    - Prostate Specific Antigen (PSA) >4.0 ng/mL

13. Presence of hepatitis B surface antigen (HBsAg), positive hepatitis C antibody test result at screening or within 3 months prior to first dose of study treatment. NOTE: Participants with positive Hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative Hepatitis C RNA PCR test is obtained.
14. QT interval corrected for heart rate by Bazett's formula (QTcB) or QT interval corrected for heart rate by Fridericia's formula (QTcF) >450 msec or QT interval corrected for heart rate (QTc) >480 msec in participants with Bundle Branch Block based on a single ECG.
15. A positive test for HIV antibody.

Other Exclusions

16. More than two moderate/severe COPD exacerbations within the past year
    - Exacerbation is defined as worsening of two or more of the following major symptoms: dyspnoea, sputum volume, sputum purulence OR worsening of any one major symptom together with at least one of the following additional symptoms: sore throat, colds (nasal discharge and/or nasal congestion), fever > 37.5°C without any explained cause, increased cough, increased wheeze.
    - A moderate exacerbation is defined as an exacerbation that requires treatment with antibiotics and/or oral steroids. A severe exacerbation is defined as an event that is additionally associated with hospitalization or emergency room visit.
17. Any moderate/severe COPD exacerbation in the 4 weeks preceding the screening visit.
18. Participants on long term oxygen therapy (LTOT), defined as prescribed continuous oxygen use for >14 hours/day.
19. Clinically diagnosed history of drug or alcohol abuse within 5 years prior to randomization.
20. History of sensitivity to any of the study medications, or components thereof or a history of drug or other allergy that, in the opinion of the investigator or GSK Medical Monitor, contraindicates their participation.
21. Participation in a formal pulmonary rehabilitation exercise program outside or inside the home, either currently or completed within the previous 6 months.
22. For participants who opt to have MRI at participating study sites, there must be no contraindications to MRI, for example known claustrophobia or a pacemaker. Specific MRI contraindications will be determined by the type of MRI scanner available at each site and study personnel should confirm local eligibility requirements.

6.3. Lifestyle Restrictions

6.3.1. Meals and Dietary Restrictions

Over the counter medications or supplements that are known to be strong inducers of CYP3A4, such as St John's Wort, should be discontinued for the duration of the study.

Except as stated above, participants should continue their regular diet for the duration of the study.

6.3.2. Caffeine, Alcohol, and Tobacco

For each visit, participants will abstain from any alcohol for 24 hours prior to the start of the visit until collection of the venous blood sample during each visit. For the duration of the study, participants should be encouraged to avoid excessive alcohol intake (defined as consumption of more than 1-2 drinks per day in the USA).

6.3.3. Activity

Participants should refrain from significant changes in their exercise level (e.g., joining a gym), except as instructed by the investigator, for the duration of the study. Participants will abstain from strenuous exercise, e.g. running, for 24 hours prior to each blood collection for clinical laboratory tests.

6.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are never subsequently randomized. A minimal set of screen information is required to ensure transparent reporting of screen failure participants, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious SAEs.

Participants are expected to meet study entry criteria when they are randomized. If a participant initially qualifies for the study and their condition changes prior to randomization such that they no longer qualify for the study, the participant should be considered a screen failure. Participants who experience a moderate/severe exacerbation of COPD in the period after the screening visit AND before the baseline visit should be considered a run-in failure, however these participants may be eligible for rescreening at a later date. Note: Participants who fail screen may be rescreened if, in the opinion of the investigator, the participant's condition was transient and the participant will qualify for the study at a later date during the study enrolment period. Participants may be rescreened a maximum of two times in total. Rescreened participants should be assigned a new participant number.

7. TREATMENTS

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

7.1. Treatments Administered

Study Treatment Name:	GSK2881078	Placebo
Dosage formulation:	Capsule	Capsule
Unit dose strength(s):	0.5mg, 1.0mg	N/A

Dosage level(s)	1.0mg for women (2 x 0.5mg capsules) once daily 2.0mg for men (2x 1.0mg capsules) once daily	2 capsules once daily
Route of Administration	For oral use only	For oral use only
Dosing instructions:	Take as directed	Take as directed
Packaging and Labeling	Capsules will be provided in a bottle. Each bottle will be labeled as required per country requirement.	Capsules will be provided in a bottle. Each bottle will be labeled as required per country requirement.

7.1.1. Medical Devices

- There are no GSK manufactured medical devices (or devices manufactured for GSK by a third party) provided for use in this study.
- Other medical devices (not manufactured by or for GSK) provided for use in this study are the Actigraph physical activity monitor, a consumer pedometer and an android tablet which will be used to administer the home exercise program and electronic PROs.
- Instructions for medical device use are provided in the study reference manual.

7.2. Dose Modification

Not applicable.

7.3. Method of Treatment Assignment

Male and post-menopausal female participants who are between 50 and 75 years of age and meet all other study entry criteria will be assigned to one of the (Male: placebo or 2.0 mg of GSK2881078; Postmenopausal female: placebo or 1.0 mg of GSK2881078) in a ratio of 1:1 in accordance with the randomization schedule generated under the auspices of Clinical Statistics at GSK, prior to the start of the study, using validated software. Separate randomizations will be generated for each gender, and the randomisation process will assign the container number for study treatment. Each participant will be dispensed blinded study treatment with unique container numbers, which will be distinct from the randomisation numbers.

If a participant experiences an exacerbation, then that participant may be replaced upon consultation with GSK. The replacement participant will receive the same treatment as the participant being replaced. The random number for the replacement participant will be 1000 + the random number for the replaced participant.

7.4. Blinding

This will be a double blind (sponsor unblind) study and the following will apply.

- The investigator or treating physician may unblind a participant's treatment assignment **only in the case of an emergency** OR in the event of a serious medical condition when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the participant as judged by the investigator.
- It is preferred (but not required) that the investigator first contacts the Medical Monitor or appropriate GSK study personnel to discuss options **before** unblinding the participant's treatment assignment.
- If GSK personnel are not contacted before the unblinding, the investigator must notify GSK as soon as possible after unblinding, but without revealing the treatment assignment of the unblinded participant, unless that information is important for the safety of participants currently in the study.
- The date and reason for the unblinding must be fully documented in the CRF

A participant will be withdrawn if the participant's treatment code is unblinded by the investigator or treating physician. The primary reason for discontinuation (the event or condition which led to the unblinding) will be recorded in the CRF.

- GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the treatment assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's treatment assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.
- Members of the GSK study team will be unblinded for in-stream data reviews and the interim analyses as appropriate. This may include the study statistician, programmers, physician project leader, Muscle Metabolism Discovery Performance Unit leader, safety review team and other decision makers. At the time of interim analysis, access to the randomization will be restricted to randomization numbers that have been assigned at the time of data cut-off.

7.5. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
2. Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. Participants should be encouraged to store study treatment in a secure environment and follow directions for storage on the drug label.

3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study treatment are provided in the Study Reference Manual.

- Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff. A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

7.6. Treatment Compliance

- When participants are dosed at the site, they will receive study treatment directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study treatment and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment.
- When participants self-administer study treatment(s) at home, compliance with GSK2881078will be assessed through querying the participant during the site visits and documented in the source documents and CRF. A record of the number of GSK2881078 tablets dispensed to and taken by each participant must be maintained and reconciled with study treatment and compliance records. Treatment start and stop dates, including dates for treatment delays and/or dose reductions will also be recorded in the CRF.
- Compliance at each visit will be determined as follows:

  (# dispensed - # returned) x 100 / (# days since last visit)
- Participants estimated to have taken less than 80% or more than 120% of study treatment capsules at two consecutive visits will be considered noncompliant. All attempts should be made to improve the participant's compliance in taking study treatment if the participant is continuing in the study.

7.7. Concomitant Therapy

Medications and therapies not specifically prohibited by the study are allowed. Study participants must be on optimal maintenance therapy for COPD prior to screening, with no change in maintenance therapy for at least 4 weeks prior to baseline measurements and no anticipated changes between baseline and end of study. Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

1. reason for use
2. dates of administration including start and end dates

3. dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Use of the following medications with study treatment is prohibited during the study:

- Cholestyramine
- Oral steroids
- Any prescription drugs known to affect muscle mass, including androgen supplements, anti-androgens (such as LHRH agonists), anti-estrogens (tamoxifen, etc.), recombinant growth hormone, megesterol, etc.
- Strong inducers of CYP3A4 such as St John's Wort, Carbamezapine, Phenytoin and Rifampicin.

Of note, weaker CYP3A4 inducers are allowed.

A more complete listing of the different classes of CYP3A4 inducers can be found at Univ of Indiana School of Pharmacy website (http://medicine.iupui.edu/clinpharm/ddis/main-table/) or FDA website (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#classInhibit).

Although no evidence of lowering of blood glucose has been seen in phase I human studies of GSK2881078, improved glycaemic control has been observed with other SARMs, e.g. GTx-024, in healthy volunteers. Although the risk of a hypoglycaemic event in participants on diabetes treatments and GSK2881078 is considered very low, participants who are on medication (either oral medication or insulin) for diabetes should be counselled to monitor their blood glucose levels (where applicable) and remain alert for hypoglycaemic events. Participants should seek medical advice to adjust their diabetes treatment if they have any concerns in conjunction with advice from the Investigator and/or the Medical Monitor.

7.8. Treatment after the End of the Study

Participants will not receive any additional treatment from GSK after completion of the study because the indication being studied is not life threatening.

The investigator is responsible for ensuring that consideration has been given to the post-study care of the participant's medical condition, whether or not GSK is providing specific post-study treatment.

8. DISCONTINUATION CRITERIA

8.1. Discontinuation of Study Treatment

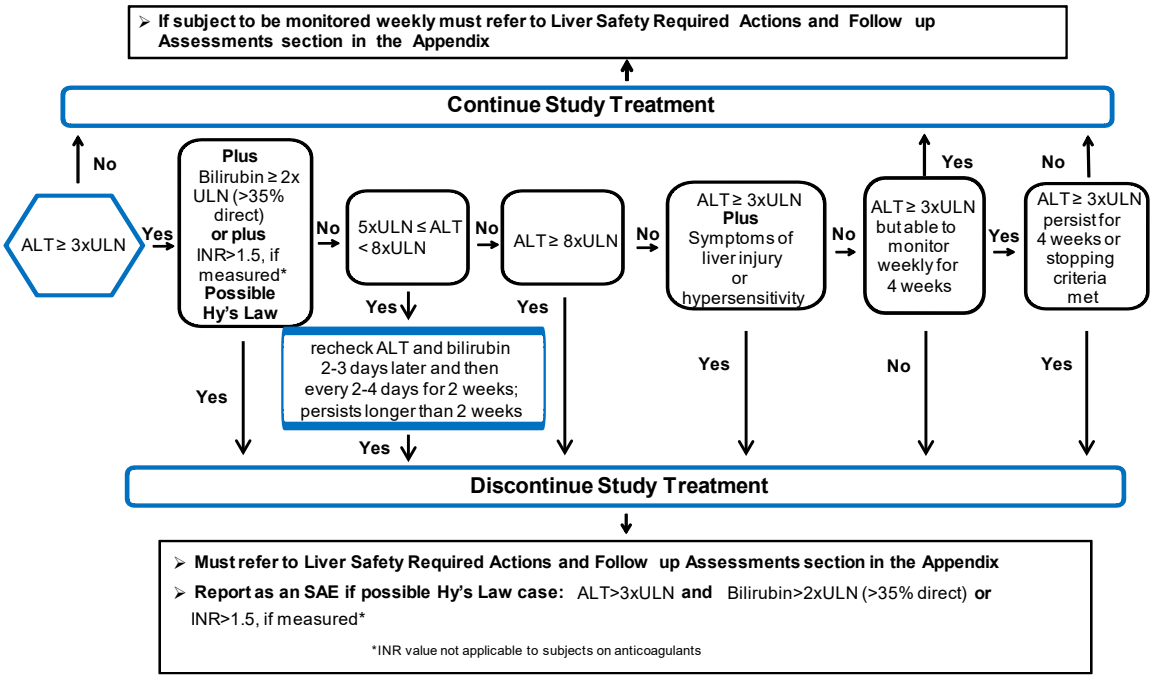
A participant may discontinue treatment if they have a severe exacerbation of COPD requiring hospitalization or if they meet liver or QTc stopping criteria. A participant who discontinues study treatment should return to the clinic only for the follow-up visit within the specified window if possible. Only the safety assessments for the follow-up visit (physical examination, 12-lead ECG, vitals, blood tests, urinalysis and concomitant medication review) should be conducted in these participants as described in the SoA and Section 9.4.

8.1.1. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Study treatment will be discontinued **for a participant** if liver chemistry stopping criteria are met:

Liver Chemistry Stopping and Increased Monitoring Algorithm



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 4 Liver Safety: Required Actions and Follow-up Assessments

8.1.2. QTc Stopping Criteria

For trial eligibility and discontinuation, ideally the same QT correction formula will be used for *all* participants within a single trial. However, GSK does recognize that because multiple sites from different countries may participate in a single trial, this may not always be possible since QT correction formulae pre-programmed by different manufacturers within ECG machines tend to vary. In these situations, the same QT correction formula must be used throughout the trial for an individual participant.

- The QTc should be based on averaged QTc values of triplicate ECGs obtained over a brief (e.g., 5-10 minute) recording period.

A participant who meets either of the bulleted criteria below will be withdrawn from the study:

- QTc >500 msec OR Uncorrected QT >600 msec
- Increase from baseline of QTc >60 msec

For participants with underlying **bundle branch block**, follow the discontinuation criteria listed below:

Baseline QTc with Bundle Branch Block	Discontinuation QTc with Bundle Branch Block
<450 msec	>500 msec
450 – 480 msec	≥530 msec

See the SoA for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

8.1.3. Temporary Discontinuation

Withdrawal of study treatment requires withdrawal from the study.

8.1.4. Study Treatment Restart or Rechallenge

Study treatment restart or rechallenge after liver chemistry stopping criteria are met by any participant in this study is not allowed.

8.2. Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance or administrative reasons.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant decides to withdraw or is withdrawn by the responsible physician, the reasons for withdrawal and the results of any relevant tests will be recorded in the CRF and the planned follow-up procedures will be performed, where possible.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
- Refer to the SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. Only the safety assessments scheduled for the follow-up visit should be conducted in these participants as described in the SoA (Section 2).
- **Any participant who experiences a severe COPD exacerbation (i.e., associated with hospitalization or emergency room visit) or an exacerbation that requires treatment with oral steroids will be permanently discontinued from study treatment and should return to the clinic for the follow-up visit within the specified window if possible. Only the safety assessments scheduled for the follow-up visit should be conducted in these participants as described in the SoA (Section 2).**

8.3. Lost to Follow Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

9. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Protocol waivers or exemptions are not allowed
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Except for the SPPB, procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA. All protocol-specified lab samples obtained from Baseline through the end of the study must be submitted to the central lab.
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 500 mL. Individual visit blood draws should not exceed 50mls. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

9.1. Study Procedure

9.1.1. Screen

Participants who meet study inclusion/ exclusion criteria will be provided with a computer tablet and physical activity monitor after signing informed consent for the study. Participants will complete a "training period" with the Daily PROactive Physical Activity in COPD instrument (Section 9.2.4.4) and Physical Activity Monitor (Section 9.2.4.5) for 1 week after screening, and will return the Actigraph activity monitor at the day -9 visit.

NOTE: If participants do not have results from the screening blood tests available on the day of screening, they may still be dispensed a computer tablet and activity monitor provided the other study inclusion/exclusion criteria are met; if participants are subsequently found to be ineligible, they must return the tablet and monitor to the study site as soon as possible and physical activity data from these participants will not be collected.

Cardiovascular medical history/risk factors (as detailed in the CRF) will be assessed at screening. The following demographic parameters will be captured: year of birth, sex, race and ethnicity. Medical/medication/family history will be assessed as related to the inclusion/exclusion criteria listed in Section 6.1. The number of previous exacerbations and history of pulmonary rehabilitation must be recorded in the CRF.

9.1.2. Day -9 and day 80 visits

The purpose of the day -9 and day 80 visits is primarily to collect 7 days of activity data from the previous visits (screening and day 56 visits respectively) and to dispense activity monitors for the following visit. Activity data and PROactive questionnaire data should be downloaded at day -9 and day 80 visits. A fully charged activity monitor and new 7 day daily PROactive instrument should be dispensed, and this data should be collected at baseline (day 1) and last dose (day 90) visits respectively.

The day -9 visit will also be used to familiarise participants with the home exercise training program, and to dispense equipment for home exercises, although participants should only begin exercises on day 1.

A practice incremental shuttle walk test (Section 9.2.3.2) should also be carried out at the day -9 visit to familiarise participants with the test prior to baseline.

9.1.3. Baseline (day 1) and last dose (day 90) visits

Details for efficacy and safety assessments can be found in Section 9.2 and Section 9.5 respectively. At some study sites, optional cardiac, liver and prostate MRI scans will be offered to eligible participants (Section 9.5.5).

Day 1 and day 90 visits should be conducted within 1 day, but participants may need to return on a separate day for the MRI and/or DXA scans, and possibly other assessments. The scans, and any other assessments, may be conducted on a separate day within the

visit window where it is not feasible to conduct these on the same day. For the baseline visit, all assessments should be carried out prior to randomization. The order for conducting all study assessments will be specified in the study reference manual (SRM).

Participants should return the Actigraph activity monitors and completed PROactive diary instruments at these visits. At day 90, participants should additionally return equipment related to the home exercise program.

All baseline and day 90 assessment should be conducted in accordance with instructions in the SoA and within Section 9. Participants should remain within the unit for observation for 1 hour following the first dose.

9.1.4. Interim visits

All assessments will be performed at the times specified in the SoA and in Section 9.2 and Section 9.5 .

9.1.5. Follow-up visit

All assessments will be performed at the times specified in the SoA and in Section 9.2 and Section 9.5. For participants who have discontinued study treatment, only safety assessments as described in Section 9.5 and the SoA should be carried out.

9.2. Efficacy Assessments

All assessments will be performed at the times specified in the SoA (Section 2) and Section 9.1.3.

9.2.1. Pulmonary Function Tests

9.2.1.1. Spirometry

Spirometry using FEV_1 and FVC measurements (FEV% predicted, and FVC% predicted and FEV_1/FVC will be calculated using the Quanjer reference equation [Quanjer, 2012]) will be performed. At least three, and no more than 8 efforts must be performed in order to obtain at least three acceptable efforts at one visit. The best of three acceptable efforts will be recorded in the CRF. Spirometry assessments should be performed in accordance with American Thoracic Society/European Respiratory Society guidelines. Spirometry will be performed at screening, baseline, day 56, and day 90. Site-specific training will be given at the site initiation visit for all sites to harmonize data collection procedures prior to participant recruitment. Assessments should be carried out on the same spirometer and by the same site personnel where possible to reduce inter-observer variation.

9.2.1.2. Sniff Nasal Inspiratory Pressure (SNIP)

Inspiratory muscle strength will be assessed by measuring the maximal SNIP [Kyroussis, 2002]. A bung size-specific to the participant is placed in the nostril deemed by the investigator to be most patent. The participant is asked to make a maximum voluntary

sniff effort via a peak flow meter and the greatest effort from 10 repeat measurements will be recorded in the CRF. The sniff meter display is visible to the participants to provide feedback. SnIP measurements will be undertaken at screening, baseline, day 56 and day 90 visits. Site-specific training will be given at the site initiation visit for all sites to harmonize data collection procedures prior to participant recruitment. Assessments should be carried out by the same site personnel where possible to reduce inter-observer variation.

9.2.2. Lean Mass measures

9.2.2.1. Dual-Energy X-ray Absorptiometry (DXA)

Participants will be asked to lie on a padded platform while a mechanical arm passes over their body; the test usually takes approximately 10-30 min. Output from these scans will be used to measure body composition including total body mass, total lean mass and fat mass. Appendicular lean mass will be calculated from the regional lean mass measurements of the arms and legs. DXA measurements will be undertaken at baseline, day 28, 56, 90 and follow-up visits.

9.2.3. Functional Assessments

All functional assessments should be performed as described in the SRM.

9.2.3.1. Leg Press

Lower extremity strength will be measured as the 1-repetition maximum (1-RM) on a leg press device.

Participants will have a warm up followed by one set of 5-10 repetitions using 40-60% of estimated maximum. Participants will then lift progressively heavier weights in steps, with each step separated by an appropriate rest period, until participant cannot complete the lift. The last successfully completed lift will be recorded as the 1-RM [LeBrasseur, 2008; Travison, 2011]. The same study personnel should perform this test wherever possible; site-specific training for this procedure will be given to harmonize data collection procedures prior to participant recruitment. Leg press measurements will be undertaken at screening, baseline, day 28, day 56, day 90 and follow-up visits.

9.2.3.2. Shuttle walk tests (Incremental shuttle walk test and endurance shuttle walk test)

Participants will perform a practice standard, incremental shuttle walk test on the day -9 visit. An incremental shuttle walk will be performed at the baseline visit and the day 90 visit to determine peak work rate. After a minimum 40 minute rest, participants will perform constant work rate testing (endurance shuttle walk test) at 85% of peak work rate from the incremental walk test conducted at the baseline visit.

Tests will be stopped when participants are unable to maintain the walking speed and/or are too tired and/or breathless to continue [Singh, 1992]. The total distance walked from

the incremental test, duration in seconds from the CWR and percentage change for both peak work rate and endurance time should be recorded.

Site-specific training for this procedure will be given to harmonize data collection procedures prior to participant recruitment.

9.2.3.3. Short Physical Performance Battery (SPPB)

Participants will be assessed for balance, timed rises from a chair, and gait speed, and scored according to published guidelines [Guralnik, 1994]. The scores for each component and the time in seconds for each component will be recorded. The same study personnel should perform this test wherever possible; site-specific training for this procedure will be given to harmonize data collection procedures prior to participant recruitment.

Short physical performance battery should be undertaken at screening, baseline, day 28, day 56 and day 90 visits.

9.2.3.4. Handgrip Strength

Handgrip strength of both hands will be measured and recorded using a hand dynamometer with participants seated, their shoulders adducted, elbows flexed to 90˚ and forearms in a neutral position. Participants will be asked to make a maximal effort to squeeze the handle and strength will be recorded to the nearest kilogram. The best of the six measurements (three measurements for each hand) will be used for the statistical analyses [Puhan, 2013].

9.2.4. Patient Reported Outcomes Assessments

9.2.4.1. COPD Assessment Test (CAT)

The CAT (www.CATestonline.org) is a validated, short (8 item), and simple patient completed questionnaire which has been developed for use in routine clinical practice to measure the general health status of patients with COPD. The CAT is designed to measure overall COPD-related health status for the initial assessment and longitudinal follow up of COPD patients. When completing the questionnaire, participants complete each question by rating their experience on a 6 point scale with anchoring statements, ranging from 0 (no impairment) to 5 (maximum impairment) with a total scoring range of 0 – 40 [Jones, 2009]. The CAT will be completed at baseline, day 56 and day 90.

9.2.4.2. St George Respiratory Questionnaire COPD (SGRQ-c)

The SGRQ-c (http://www.healthstatus.sgul.ac.uk/SGRQ_download/sgrq-c-manual-april-2012.pdf) has been developed using COPD data only to measure general health related quality of life, and is a validated questionnaire for COPD. It consists of 40 items in total, corresponding to 3 individual domains: symptoms, activity and impact, with different components carrying a different weighting. The score range is from 0 (no impairment) to a theoretical maximum of 3201.9 for the worst possible state of the participant. The

minimal clinically important difference for a change in SGRQ-c is 4.0 points [Jones , 2005]. The SGRQ-c will be completed at baseline and day 90.

9.2.4.3. Patient Global Rating of Severity (PGRS) and Patient Global Impression of Change (PGIC)

The PGRS is a single global question that asks participants to rate how their condition impacts their ability to perform physical activity on a five-point scale (none, mildly, moderately, severely, very severely).

Responses to the PGIC question will be on a 7 point Likert scale ranging from much better to much worse.

The PGRS will be completed only at baseline and day 90. However, the PGIC will be completed at day 14, 28, 56, 90 and at the follow up visit.

9.2.4.4. Daily PROactive Physical Activity in COPD instrument (D-PPAC)

The Daily PROactive instrument is a hybrid outcome assessment tool comprising an electronic diary and outputs from a triaxial physical activity monitor (described in 9.2.4.5) which has been assessed as compatible with PROactive. The electronic diary consists of 7 questions to be completed each evening. The output from the e-diary is combined with two summary outputs from the activity monitor to produce the PROactive score.

The PROactive tools were developed by a consortium funded by the European Union Innovative Medicines Initiative (IMI) (JU115011) using well accepted methodologies. The PROactive consortium included pharmaceutical companies, academic institutions and patient organisations from across Europe (www.proactivecopd.com). Following systematic reviews of determinants and outcomes of physical activity [Gimeno-Santos, 2014] available patient reported measures of activity [Gimeno-Santos, 2011; Williams, 2012; Frei, 2011] and performance of activity monitors [Van Remoortel, 2012] the components of the tool were developed.

The original activity monitors included in the PROactive trials were chosen based on performance in COPD patients across a range of disease severity [Van Remoortel, 2012; Rabinovich, 2013]. Activity monitors assessed as compatible for use in the PROactive tools are assessed against this standard.

Development of the electronic diary was patient centred and also involved physician interviews [Dobbels, 2014]. The items included in the final diary were finalised using a structured, rigorous scientific approach in the item reduction process to select the best items and generate the final questionnaire. The psychometric properties of the PROactive tool and responsiveness were determined in a program of studies conducted by consortium members [unpublished data].

The fit of the PROactive tool for this indication and population will be assessed in a separate validation exercise and via the exit interviews in this study.

9.2.4.5. Physical Activity Monitor

Physical activity limitation is a common feature of COPD and its measures are highly related to the degree of disease severity as assessed by airflow limitation, dyspnoea, and overall health status [Watz, 2009]. Studies have reported that a low level of daily activity in COPD is associated with an increased risk of hospital admissions for acute exacerbations of COPD, morbidity and mortality [Bourgeois, 2011; Waschki, 2011]. Increased activity has been identified as an important factor that may modify morbidity and mortality in COPD [Moy, 2012]. A recent ECLIPSE sub study in COPD participants demonstrated the potential application of physical activity monitors in multicenter clinical trials [Waschki, 2012].

A clinically validated physical activity monitor (accelerometer) will be used to measure levels of activity. The physical activity monitor will be worn for 7 days by the study participants at 4 time points during the study to provide the total PROactive score. A separate consumer based pedometer will be worn at the wrist throughout the study treatment period to count the daily number of steps in conjunction with the home exercise program.

In addition to a period of familiarization with the physical activity monitor after screening, there will be 3 assessment periods, including an initial baseline assessment in order to provide a reliable estimate of habitual physical activity. Further details will be provided in the SRM.

Physical activity monitors will be shipped from each study site directly to GSK for analysis and interpretation or to an independent vendor, contracted by GSK, blinded to treatment assignment, who will be responsible for transmitting the data to GSK and returning the devices to the sites.

9.2.4.6. Patient Exit Interview

An exit interview will be administered by experienced interviewers (by a partner agency) at the end of the study. The questions included in the interview are designed to more fully understand the participant's experience with the study medication and the study itself. Interviewers will usea semi-structured interview guide and data collection sheet and responses will be audio-recorded for purposes of accurate analysis; exit interview data will be recorded and reported separately to the main study report.

9.2.5. Home Exercise Program

A home exercise program will be administered via an application developed by GSK. The application gives customised instruction to participants to incrementally increase their physical activity (via monitoring step counts) and strength (through a combination of strengthening exercises). Exercises are demonstrated on videos in the application as well as via written instruction; participants will be further given training on using the application by site staff, who will assess their baseline ability to perform all exercises in addition to providing instruction.

9.3. Adverse Events

The definitions of an AE or SAE can be found in Appendix 5.

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue the study treatment or the study (see Section 8).

Planned time points for all safety assessments are listed in the SoA (Section 2). Additional time points for safety tests (such as vital signs, physical exams and laboratory safety tests) may be added during the course of the study based on newly available data to ensure appropriate safety monitoring.

9.3.1. Time Period and Frequency for Collecting AE and SAE Information

- All SAEs will be collected from start of treatment until the follow-up visit at the time points specified in the SoA (Section 2).
- All AEs will be collected from the start of treatment until the follow-up visit at the time points specified in the SoA (Section 2).
- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the CRF not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix 5. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.
- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 5.

9.3.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

Appropriate questions include:

- "How are you feeling
- "Have you had any (other) medical problems since your last visit/contact?"
- "Have you taken any new medicines, other than those provided in this study, since your last visit/contact?"

9.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Appendix 5.

9.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information eg, summary or listing of SAE) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

9.3.5. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 5 and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the CRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The CV CRFs are presented as queries in response to reporting of certain CV medical dictionary for regulatory activities (MedDRA) terms. The CV information should be

recorded in the specific cardiovascular section of the CRF within one week of receipt of a CV Event data query prompting its completion.

The Death CRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within one week of when the death is reported.

9.3.6. Pregnancy

- Female participants of child bearing potential are excluded from this study.
- If a pregnancy is reported, the investigator should inform GSK within 2 weeks of learning of the pregnancy and should follow the procedures outlined in Appendix 2.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

9.4. Treatment of Overdose

For this study, any dose of GSK2881078 greater than 1.0mg for females and 2.0mg for males within a 24-hour time period will be considered an overdose.

GSK does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator/treating physician should:

1. Contact the Medical Monitor immediately.
2. Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

9.5. Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

9.5.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the Skin, Head, Eyes, Ears, Nose, Throat, Thyroid, Cardiovascular, Respiratory, Gastrointestinal, Neurological, lymph nodes and extremities. Height and weight will also be measured and recorded; height measurements should be undertaken without shoes and for weight measurements, participants should remove outdoor clothing.

- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen. Other brief physical examinations in this study may be conducted at the discretion of the Investigator for safety reasons (other than at screening or early withdrawal/follow-up). A full physical examination may be performed in lieu of a brief examination, at the discretion of the Investigator.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

9.5.2. Vital Signs

- Skin temperature, pulse rate, respiratory rate, and BP will be assessed.
- Blood pressure and pulse measurements will be assessed in a seated position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).

Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 3 BPmeasurements (3 consecutive BP readings will be recorded at intervals of at least 1 minute). The average of the 3 BP readings will be recorded on the CRF.

9.5.3. Electrocardiograms

- 12-lead ECGs in triplicate will be obtained as outlined in the SoA using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 8.1.2 for QTc withdrawal criteria and additional QTc readings that may be necessary. The same ECG machine and QTc correction factor should be used for all assessments in an individual participant.
- At each time point at which triplicate ECG are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart.

9.5.4. Clinical Safety Laboratory Assessments

- Refer to Appendix 6 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 42 days after the last dose of study treatment should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or medical monitor.
- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 6, must be conducted in accordance with the laboratory manual and the SoA. Refer to the Laboratory Manual for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.
- If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded in the relevant section of the CRF, e.g. the SAE form.

9.5.5. MRI scans (Optional sub-study)

- Pre-specified study sites will offer an optional cardiac, liver and prostate, where applicable, MRI to eligible participants. MRI will be undertaken in participants who consent at the baseline (day 1) and last dose (day 90) visits.
- In participants who agree to the MRI scans, every effort should be made to conduct all applicable MRI scans (cardiac and liver MRI for female participants, and additionally a prostate MRI for male participants). In circumstances where it is not feasible to continue performing all the MRI scans (e.g. patient discomfort), the cardiac scan should be prioritized over the liver or prostate scans.
- The protocol for the MRI scans can be found in the SRM.
- The clinical report for the MRI should be reviewed by the investigator, and the review, together with any resulting actions, documented and filed in the CRF within 2 weeks of the MRI scan.
- If results from the MRI require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded in the CRF.

9.6. Pharmacokinetics

- Blood samples of approximately 2 mL will be collected for measurement of plasma concentrations of GSK2881078 as specified in the SoA. Every effort should be made to collect samples at times throughout the time window (i.e., avoid collections from all subjects at the same time within a window or only at the extremes of a window).

- Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded in the eCRF. Times of dose administration for the two doses immediately preceding a PK sample should be accurately recorded in the eCRF.
- Samples will be used to evaluate the PK of study treatment. Samples collected for analyses of study treatment plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- Genetic analyses will not be performed on these plasma samples. Participant confidentiality will be maintained.
- Once the plasma has been analyzed for parent compound, any remaining plasma may be analyzed for other compound-related metabolites and the results reported under a separate protocol.

Drug concentration information that may/would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

9.7. Genetics

A 6 mL blood sample for DNA isolation will be collected from participants who have consented to participate in the genetics analysis component of the study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

See Appendix 7 for Information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in the Study Reference Manual.

9.8. Biomarkers

- Collection of samples for other biomarker research is also part of this study. Blood samples for biomarker research are required and will be collected from all participants in this study as specified in the SoA.
- Samples will be tested for reproductive tissue biomarkers, bone biomarkers and exploratory biomarkers to evaluate their association with the observed clinical responses to 2881078.
- Other samples may be used for research to develop methods, assays, prognostics and/or companion diagnostics related to 2881078, COPD and/or sarcopenia, pathways associated with disease state, and/or mechanism of action of the study treatment.

9.8.1. Reproductive Tissue Biomarkers

- luteinizing hormone

- follicle stimulating hormone
- total testosterone
- free testosterone (calculated) in males and females
- estradiol (females)
- dihydrotestosterone
- sex hormone binding globulin
- prostate specific antigen (PSA) males

9.8.2. Bone Biomarkers

- procollagen type I N propeptide (s-PINP)
- C-terminal telopeptide of type I collagen (s-CTX)

9.8.3. Exploratory Biomarkers

Blood samples (approximately 10 mL) will be collected at each timepoint indicated in the SoA (Section 2), such as proteins related to anabolic effects on muscle. These samples will be analyzed separately. These results will not be reported as part of this study. See SRM for further details.

10. STATISTICAL CONSIDERATIONS

Unblinded data will be reviewed in-stream by the study team. A Bayesian predictive approach using a non-informative prior will be used for the assessment of futility of the strength endpoint at an interim analysis. Although strength is the primary endpoint for the assessment of futility, the decision to continue or stop recruitment will be based on the totality of the data including strength, lean mass, functional endpoints, safety and tolerability.

After study completion, a Bayesian analysis using non-informative priors will be used to estimate posterior and posterior predictive distributions, as appropriate, for strength, lean mass and the functional endpoints to inform decision making. A multivariate Bayesian approach will be employed, data permitting

In addition, the effects of GSK2881078 relative to placebo on strength, lean mass and functional endpoints (i.e., incremental and endurance shuttle walk tests, and SPPB) will be evaluated using an estimation approach where point estimates and associated 90% confidence intervals (CI) will be constructed.

Descriptive statistics will be used to address safety, tolerability, PRO and PK objectives.

Data for male and female subjects will be analyzed separately. Depending on recruitment rates, analysis and reporting may be completed at different times for males and females.

10.1. Sample Size Determination

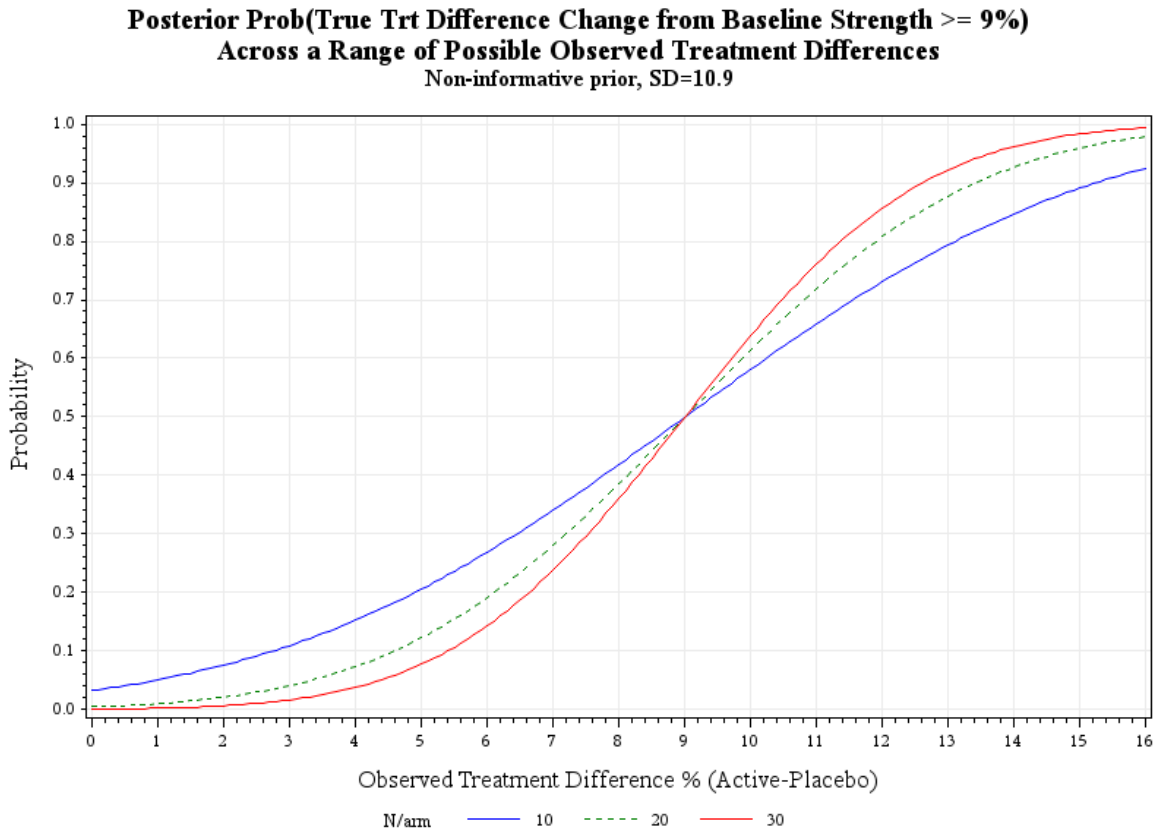
10.1.1. Sample Size Assumptions

The sample size was determined using an estimation approach in order to provide sufficient precision for the estimation of the strength endpoint in particular, with consideration also given to lean mass and the functional parameters. In addition, the influence of the sample size on the estimated posterior probability (true treatment difference in change from baseline strength ≥ 9%) was evaluated. An increase in strength of 9% or more is of interest because it is consistent with effects observed with testosterone treatment [Casaburi, 2004 ; Sheffield-Moore, 2011; Bhasin, 2005]. Since different doses of GSK2881078 will be administered to males and females, all analyses will be conducted separately for each sex. Sample sizes of 10 (interim) and 20 per treatment group yield the following precision.

Primary Endpoint		**Change from Baseline**
	n	Strength (%)
Target Effect[1] (ΔΔ)		9
SD[2]		10.9
Half-width of 90% CI for ΔΔ	10	8.45
	20	5.8

[1]ΔΔ refers to difference from placebo in change from baseline. Strength [Casaburi, 2004] and data provided by author; [Sheffield-Moore, 2011; Bhasin, 2005]; [2] Strength, data provided by author];

The sample size also supports the evaluation of the posterior probability (assuming a non-informative prior) that the true treatment difference in change from baseline strength ≥ 9% as illustrated in the graph below. Note a greater benefit is achieved by increasing the sample size from 10 to 20 than from 20 to 30.



For the secondary functional endpoints (ISWT, ESWT), it is uncertain what magnitude of effect would translate into a meaningful benefit to the participant. Therefore, the target effects listed below should be considered exploratory. A range of targets, including those indicated below will likely be evaluated.

Secondary Endpoints		**Change from Baseline**		
	N	**Total Lean mass (kg)**	**ISWT (m)**	**ESWT (s)**
Target Effect[1] (ΔΔ)		2	28.5 or 47.5	132 or 186
SD[2]		2.5	57	265
Half-width of 90% CI for ΔΔ	10	1.94	44.2	206
	20	1.33	30.4	141

[1]ΔΔ refers to difference from placebo in change from baseline. Lean mass [Casaburi, 2004] and data provided by author; [Sheffield-Moore, 2011; Bhasin, 2005]; ISWT estimated as ½ SD from unpublished GSK data or suggested by [Singh, 2008] ESWT estimated as ½ SD from unpublished GSK data or suggested by [Altenburg, 2015]; [2] Lean mass, and data provided by author]; ISWT and ESWT from unpublished GSK data

10.1.2. Sample Size Sensitivity

Sample size sensitivity analyses are described above.

10.1.3. Sample Size Re-estimation or Adjustment

Based on the observed variability and treatment effects at an interim analysis, the sample size may be increased to improve the precision of the estimates of treatment effects and the operating characteristics of the end of study decision criteria. Strength, ISWT and ESWT will be considered in the sample size evaluation. Males and females will be evaluated separately. The sample size may be increased by up to 15 subjects/arm.

Details of the interim analysis will be described in the Reporting and Analysis Plan (RAP).

10.2. Populations for Analyses

All Participants Population

The 'All Participants Population' is defined as all randomized participants who receive at least one dose of study medication.

Analysis Population

The 'Analysis Population' (AP) is defined as participants in the 'All Participants' population having baseline and at least one post-baseline assessment of the strength, lean mass or functional endpoint.

Per Protocol Population (PP)

The 'Per Protocol Population' will consist of any AP participants who are compliant with protocol-specific criteria and who do not experience an exacerbation during the treatment phase of the study. Participants with specified protocol deviations and those failing to complete the Week 13 functional assessments will be excluded. The Per Protocol population will be used for analysis of strength, lean mass and the functional endpoints.

Pharmacokinetic (PK) Population

The 'PK Population' is defined as participants in the 'All Participants' population for whom a PK sample was obtained and analysed for GSK2881078.

All available data will be used in the analyses as defined in the Populations above. Missing values will not be imputed.

10.3. Statistical Analyses

All analyses will be performed separately for females and males.

10.3.1. Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	**Strength** Change from baseline and percent change from baseline strength will be analyzed separately using mixed models repeated measures(MMRM) models with effects for treatment, day, treatment x day, and baseline strength. Differences in least squares means between the GSK2881078 treated group and placebo will be calculated (i.e.; GSK2881078- placebo) along with associated 90% CIs. The same model will be used at both the interim analysis and at the end of the study. The analyses will be performed using all available data from participants in both the AP and the Per Protocol Population. The effects of potential predictors of response including, but not limited to, baseline vitamin D levels and measures of pulmonary function may also be explored. At the interim, the posterior predictive distribution for % change from baseline strength will be estimated. This distribution will be used to estimate the probability that the end of study treatment difference will be $\geq 9\%$. Similarly, at study completion, the posterior distribution will be estimated and used to estimate the probability that the true treatment difference is $\geq 9\%$. Because % change endpoints often demonstrate a lack of normality, a supportive analysis will be performed where log-transformed strength is considered the dependent variable and log-transformed baseline the covariate using a MMRM model as described above. Differences in least squares means between each GSK2881078 treated group and placebo (i.e.; GSK2881078- placebo) along with associated 90% CIs will be constructed. The point estimates and CIs will be back-transformed (exponentiated) to provide point estimates and CIs for the ratios, GSK2881078 to Placebo. Model and distributional assumptions underlying each analysis will be assessed by visual inspection of residual plots. Parameters will be log-transformed prior to analysis if necessary to meet assumptions. If assumptions are still not met after log-transformation alternative methods of analysis will be considered. Complete details will be provided in the RAP. Any changes to the planned analyses described here will be documented in the study RAP and/or the Clinical Study Report.
Exploratory	Will be described in the reporting and analysis plan

10.3.2. Safety Analyses

All safety analyses will be performed on the Safety Population.

Endpoint	Statistical Analysis Methods
Primary	Safety data will be presented in tabular and/or graphical format and summarized descriptively according to GSK's Integrated Data Standards Library (IDSL) standards. No formal statistical comparisons will be made for the safety data. Complete details will be documented in the RAP.
Exploratory	Will be described in the reporting and analysis plan

10.3.3. Other Analyses

Descriptive summaries and graphical displays will be prepared for measures of respiratory function (FEV1, SnIP).

The relationships between changes in lean mass or strength and other endpoints including but not limited to functional measures, PROs, and activity measures will be explored.

A multivariate Bayesian approach using non-informative priors will be employed, data permitting, to further explore the relationships between changes in strength and lean mass and the functional outcomes (ISWT, ESWT,) and to inform decision making. Details of the analysis will be described in the Reporting and Analysis Plan (RAP).

10.3.4. Interim Analyses

The Reporting and Analysis Plan will describe the planned interim analyses in greater detail.

In-Stream Review

Safety, tolerability, strength, lean mass, and functional endpoint data will be reviewed by the GSK study team on an ongoing basis throughout the study for the purpose of internal decision making. These reviews can include individual participant data, summaries by treatment group and graphical displays. GSK staff will be unblinded (See Section 7.3). Participants and all site personnel will be blinded to participant randomization.

Preliminary safety, strength, lean mass, functional endpoint and PK results may be reported prior to database freeze for the purposes of safety review by GSK and where required by regulatory bodies.

Interim Analysis

An interim analysis for the assessment of futility is planned. It is anticipated that a formal declaration of futility would not be made before at least 10 participants per group have completed dosing and all key study assessments. However, if at any time it is determined

that the probability of a successful outcome is sufficiently low, recruitment could be stopped. The primary endpoint for assessment of futility is strength. However, the decision to continue or stop recruitment will be made by the unblinded GSK clinical study team and SRT based on the evaluation of all available safety, efficacy, and tolerability data. Such decisions will be based on the totality of the data (including strength, lean mass, function, safety, and tolerability). The feasibility of making a decision to stop recruitment based on a futility analysis will be dependent on the recruitment rate. Whether recruitment is suspended for the interim analysis will be dependent on the recruitment rate. Assessment of futility will be done separately for female and male participants. A Bayesian predictive approach using a non-informative prior will be used to assess the futility of % change from baseline strength at 13 weeks.

The futility criteria for strength will be based on the posterior predictive probability at the interim that the end of study difference in % change from baseline strength between GSK2881078 and placebo will achieve a positive outcome (≥9%). If the predicted probability of achieving this positive outcome is too low in the context of all available data, then enrolment into the treatment arm(s) or cohort may be stopped.

Simulations have been conducted to investigate the operating characteristics (statistical properties) of different futility criteria across a range of true treatment differences between GSK2881078 and placebo. More details on this procedure will be provided in the RAP.

As described in Section 10.1.3, the sample size may be increased to improve the precision of the estimates of treatment effects based on the observed variability and treatment effects at an interim analysis. This assessment will be done separately for males and females.

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

AE	Adverse Event
ALT	Alanine Aminotransferase
AP	Analysis Population
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
AUC	Area under concentration-time curve
AUC(0-t)	Area under the concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration within a participant across all treatments
AUC(0-tau)	Area under the concentration-time curve over the dosing interval
BMI	Body Mass Index
BP	Blood Pressure
CAT	COPD Assessment Test
CI	Confidence Interval
Cmax	Maximum observed concentration
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
CPK	Creatine phosphokinase
CRF	Case Report Form
CV	Cardiovascular
CWR	Constant Work Rate
CYP3A4	cytochrome P-450 isoenzyme 3A4
DNA	Deoxyribonucleic acid
D-PPAC	Daily PROactive Physical Activity in COPD
DXA	Dual-energy X-ray Absorptiometry
ECG	Electrocardiogram
ESWT	Endurance shuttle walk test
FDA	United States Food and Drug Administration
FEV_1	The amount of air which can be forcibly exhaled from the lungs in the first second of a forced exhalation
FSH	Follicle Stimulating Hormone
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GFR	Glomerular Filtration Rate
GSK	GlaxoSmithKline
HBsAg	Hepatitis B Surface Antigen
IB	Investigator's Brochure
HDL	High-Density Lipoprotein (cholesterol)
HIV	Human Immunodeficiency Virus

ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDSL	Integrated Data Standards Library
IEC	Independent Ethics Committee
IMI	Innovative Medicines Initiative
IRB	Institutional Review Board
ISWT	Incremental shuttle walk test
LBM	Lean Body Mass
LDH	Lactate Dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model Repeated Measures
MSDS	Material Safety Data Sheet
1-RM	1-repetition maximum
PD	Pharmacodynamic
PK	Pharmacokinetic
PGIC	Patient Global Impression of Change
PGRS	Patient Global Rating of Severity
PP	Per Protocol Population
PRO	Patient Reported Outcomes
PSA	Prostate Specific Antigen
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate by Bazett's formula
QTcF	QT interval corrected for heart rate by Fridericia's formula
RAP	Reporting and Analysis Plan
SARM	Selective Androgen Receptor Modulator
SAE	Serious Adverse Event
s-CTX	C-terminal telopeptide of type I collagen
SNIP	Sniff Nasal Inspiratory Pressure
s-PINP	Procollagen type I N propeptide
SPPB	Short Physical Performance Battery
SRM	Study Reference Manual
SRT	Safety Review Team
ULN	Upper Limit of Normal (reference range for laboratory)

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
Actigraph

12.2. Appendix 2: Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below)

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with ONE of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   Note: Documentation can come from the site personnel's: review of participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Female participants

Female participants of childbearing potential are not eligible to participate.

Male participants

- Male participants with female partners of child-bearing potential are eligible to participate if they agree to ONE of the following during the protocol-defined time frame in Section 6.1:
  - Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-

ovulation methods), declaration of abstinence for the duration of a trial, and withdrawal are not acceptable methods of contraception.

- Agree to use a male condom plus an additional method of contraception with a failure rate of <1% per year as described in Table 1 when having penile-vaginal intercourse with a woman of childbearing potential

- Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during the protocol-defined time frame
- Refrain from donating sperm for duration of study and for 4 months from last dose

Table 1 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] • oral • intravaginal • transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation[b] • injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • bilateral tubal occlusion
Vasectomized partner *(A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.)*
Sexual abstinence (*Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*

NOTES:

a. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.
b. Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. In this case two highly effective methods of contraception should be utilized during the treatment period and for at least 125 days, corresponding to time needed to eliminate study treatment plus 30 days for study treatments with genotoxic potential] after the last dose of study treatment

Collection of Pregnancy Information

Male participants with partners who become pregnant

- Investigator will attempt to collect pregnancy information on any male participant's female partner of a male study participant who becomes pregnant while participating in this study. This applies only to participants who receive study treatment.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 hours of learning of the partner's pregnancy.
- Partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK
- Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

12.3. Appendix 3: Study Governance Considerations

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
    - Applicable ICH Good Clinical Practice (GCP) Guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
    - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
    - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of

informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- Participants who are rescreened are required to sign a new ICF.

The ICF may contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research in accordance with SOP-GSKF-410. The investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate will not provide this separate signature.

Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and

not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Dissemination of Clinical Study Data

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study participants, as appropriate.

GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.

The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK Policy 408.

Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 7 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the

written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the Trial Master File.

Study and Site Closure

GSK or its designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study treatment development

12.4. Appendix 4: Liver Safety: Required Actions and Follow-up Assessments

Liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event aetiology (in alignment with the FDA premarketing clinical liver safety guidance). http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

Liver chemistry stopping criteria and required follow up assessments

Liver Chemistry Stopping Criteria – Liver Stopping Event	
ALT-absolute	ALT ≥ 8xULN
ALT Increase	ALT ≥ 5xULN persists for ≥2 weeks
ALT Increase	ALT ≥ 3xULN persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin)
INR[2]	ALT ≥ 3xULN **and** INR>1.5, if INR measured
Cannot Monitor	ALT ≥ 3xULN and cannot be monitored weekly for 4 weeks
Symptomatic[3]	ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Required Actions and Follow up Assessments following ANY Liver Stopping Event	
Actions	**Follow Up Assessments**
• **Immediately** discontinue study treatment • Report the event to GSK **within 24 hours** • Complete the liver event CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform liver event follow up assessments • Monitor the subject until liver chemistries resolve, stabilize, or return to within baseline (see **MONITORING** below) • **Do not restart/rechallenge** subject with study treatment unless allowed per protocol and GSK Medical Governance approval **is** granted. • If restart/rechallenge **not allowed per protocol**	• Viral hepatitis serology[4] • Blood sample for pharmacokinetic (PK) analysis, obtained within 14 days after last dose[5] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). • Fractionate bilirubin, if total bilirubin≥2xULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form

or not granted, permanently discontinue study treatment and may continue subject in the study for any protocol specified follow up assessments **MONITORING:** **<u>For bilirubin or INR criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hrs** • Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **<u>For All other criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	• Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake case report form **<u>For bilirubin or INR criteria:</u>** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]). • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **and** INR>1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
5. PK sample may not be required for subjects known to be receiving placebo or non-GSK comparator treatments.) Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

Liver chemistry increased monitoring criteria with continued therapy

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
ALT ≥3xULN and <5xULN **and** bilirubin <2xULN**, without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks	• Notify the GSK medical monitor **within 24 hours** of learning of the abnormality to discuss subject safety. • Subject can continue study treatment • Subject must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline • If at any time subject meets the liver chemistry stopping criteria, proceed as described above • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline.
ALT ≥5xULN and <8xULN **and** bilirubin <2xULN**, without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 2 weeks	• Notify the GSK medical monitor **within 24 hours** of learning of the abnormality to discuss subject safety. • Subject can continue study treatment • Subject must return 2-3 days after the initial observation and then return every 2-4 days for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline • If at any time subject meets the liver chemistry stopping criteria, proceed as described above • If, after 2 weeks of monitoring, ALT <5xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline.

References

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, Davern TJ, Lee WM. Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. Drug Metab Dispos 2009; 37:1779-1784.

12.5. Appendix 5: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study treatment, whether or not considered related to the study treatment. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study treatment.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of

the disease/disorder being studied, unless more severe than expected for the participant's condition.

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

g. Is associated with liver injury <u>and</u> impaired liver function defined as:

- ALT ≥ 3xULN and total bilirubin* ≥ 2xULN (>35% direct), **or**
- ALT ≥ 3xULN and INR** > 1.5.

* Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥ 3xULN and total bilirubin ≥ 2xULN, then the event is still to be reported as an SAE.

h. ** INR testing not required per protocol and the threshold value does not apply to participants receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.

Recording AE and SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK /AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficiently discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe.

  An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** GSK**.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings including histopathology. • New or updated information will be recorded in the originally completed CRF. • The investigator will submit any updated SAE data to t GSK within 24 hours of receipt of the information.

Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool
• The primary mechanism for reporting SAE to GSK will be the electronic data collection tool. • If the electronic system is unavailable for more than 24 hours, then the site will use the paper SAE data collection tool (see next section). • The site will enter the SAE data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the medical monitor/SAE coordinator by telephone. • Contacts for SAE reporting can be found in the study reference manual.

SAE Reporting to GSK via Paper CRF
• Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the **medical monitor or the SAE coordinator**. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames. • Contacts for SAE reporting can be found in the study reference manual.

12.5.1. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:
Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs: • Myocardial infarction/unstable angina • Congestive heart failure • Arrhythmias • Valvulopathy • Pulmonary hypertension • Cerebrovascular events/stroke and transient ischemic attack • Peripheral arterial thromboembolism • Deep venous thrombosis/pulmonary embolism • Revascularization

12.6. Appendix 6: Clinical Laboratory Tests

- The tests detailed in Table 2 will be performed by the central laboratory, but liver chemistry will be assessed both locally and centrally.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study treatment administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study treatment decision or response evaluation, the results must be entered into the CRF.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 6 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 2 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH MCHC? %Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[1]	BUN	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Fasting glucose	Calcium	Alkaline phosphatase	Albumin
	Phosphorous	Bicarbonate		
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones by dipstick			

Laboratory Assessments	Parameters
	• Microscopic examination (if blood or protein is abnormal)
Other Screening Tests	• Follicle-stimulating hormone (as needed in women of non-childbearing potential only) • Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody) . Note that if second generation Hepatitis C antibody positive, a hepatitis C antibody Chiron RIBA immunoblot assay (or other third generation immunoassay) should be reflexively performed on the same sample to confirm the result.
Other screening, baseline and post-baseline tests	• 25-OH Vitamin D Total, 25-OH Vitamin D2, 25-OH Vitamin D3 • Hba1c • hsCRP • Fibrinogen • luteinizing hormone • follicle stimulating hormone • testosterone • free testosterone (calculated) • estradiol (females only) • PSA in males • dihydrotestosterone • sex hormone binding globulin • Lipid panel (total cholesterol, HDL, LDL, triglycerides)

NOTES :

1. Details of Liver Chemistry Stopping Criteria and Required Actions and Follow-Up Assessments after liver stopping or monitoring event are given in Section 8.1.1 and Appendix 4
2. PK samples for events or events of special interest will be collected
3. All study-required laboratory assessments will be performed by a central laboratory.
4. The results of each test must be entered into the CRF

12.7. Appendix 7: Genetics

USE/ANALYSIS OF DNA

- Genetic variation may impact a participant's response to therapy, susceptibility, severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis
- DNA samples will be used for research related to 2881078 or COPD/ sarcopenia and related diseases. They may also be used to develop tests/assays including diagnostic tests) related to 2881078 (or study treatments of this drug class), and COPD/ sarcopenia. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).
- DNA samples will be analyzed if it is hypothesized that this may help further understand the clinical data.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to 2881078 or study treatments of this class. The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on 2881078 (or study treatments of this class) or COPD/sarcopenia continues but no longer than 15 years or other period as per local requirements.